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The causes and effects of socio-demographic exclusions from clinical trials

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Abstract

The causes and effects of socio-demographic exclusions from clinical trials

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Objectives: To investigate the exclusion from trials of women, older people and minority ethnic groups, focusing on two drug exemplars, statins and non-steroidal anti-inflammatory drugs (NSAIDs).

Data sources: Medical and ethical databases. Workshops with stakeholders.

Review methods: Literature was reviewed on exclusions in healthcare research and three workshops were held with stakeholders. Twenty-seven randomised controlled trials (RCTs) of statins use for secondary prevention of coronary heart disease (CHD) and 25 NSAIDs trials for pain in osteoarthritis (OA) were analysed. Using a Scottish cohort with record-linkage, profiling was carried out for 3188 people needing secondary prevention for CHD (1993–1996), ascertaining the independent effects of statins, and 131,410 people dispensed NSAIDs (1989–1996), examining adverse effects. Routine data sources were accessed to profile the need for secondary prevention of CHD in England and usage was estimated by consulting published surveys. The Somerset and Avon Survey of Health (SASH) 1996–97 and published data were accessed for information on potential need and usage of NSAIDs in OA. For both drugs, the socio-demographic profiles of trial samples, the population in potential need and those on treatment were compared. An evidence synthesis was produced to clarify the effects of statins on women and older people and the relationship of absolute effectiveness outcomes with underlying risk levels of disease events was modelled, examining the likely effects of trial exclusions.

Results: The average age of statins trial participants was 58.5 years; only 16.3% were women. Statins reduced cardiovascular disease (CVD) incidence by about 25% in both men and women. Older people up to 75 years of age also benefited. Meta-analysis and two landmark trials confirmed these results. The average age of NSAIDs trial participants was 61.9 years and women were well represented (68.5%). Gastrointestinal (GI) adverse events were commonly reported, but renal side-effects were not. Outcomes were seldom reported according to socio-demographic group. For both drugs, USA trials were more inclusive than UK/European trials. Ethnicity was not well reported for either drug. Some 23% of the cohort were treated with statins. Users were younger than non-statins users (but no more likely to be male) and had superior outcomes. High current exposure to NSAIDs elevated the risk of GI side-effects by about 50% versus no current exposure and renal impairment risk by nearly 140%. Side-effect risk increased with age; being female diminished risk. Approximately 537,000 incident cases of CVD would qualify for statins use in England each year. Women constitute 45% of this population with need, two-thirds of whom are aged 65 years or over. Need varies by ethnic group. No sex bias in prescribing statins was detected, but use was commoner in younger people. For NSAIDs, 6.3% of adults aged 35+ years reported hip and/or knee pain associated with OA; 3.9% of adults used prescribed analgesics for this and they were more likely to be women and to be >65 years old. For statins, women formed almost half of the 'with need' and 'on

treatment' populations, but were markedly under-represented in trials. Those aged 65+ years formed nearly two-thirds of the 'with need' population, but only one-fifth of trial samples, and were less likely to be treated than younger subjects. For NSAIDs, women formed similar proportions. Associations of side-effects with socio-demographic factors was revealed in cohort data but not in trials.

Conclusions: The issue of exclusion from trials of women, older people and ethnic minorities has been relatively neglected in the UK research community, and there is confusion about diversity issues. Under-representation occurs, but in drug trials at least this may not always affect the external validity of relative effect estimates. However, measures of absolute effectiveness, absolute harm and cost-effectiveness are associated with underlying risk levels in different socio-demographic groups. Under-representation will therefore bias absolute effect estimates. The following areas are suggested for future research: multi-disciplinary assessment of realistic options for trialists to address the issue of exclusions; clarification of the use of ethnic categories in health research and of the implications of the different dimensions of ageing and sex/gender; identification of barriers and facilitators to the involvement of different population groups in research, further investigation of the susceptibility of older men to NSAID adverse events, and the development of a 'register of registries and databases' and exploration of how linked health information systems in the UK could be improved.

Contents

List of abbreviations

ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
CABG	coronary artery bypass graft
CHD	coronary heart disease
CI	confidence interval
CTT	Cholesterol Treatment Trialists
CVD	cardiovascular disease
FDA	Food and Drugs Administration
GI	gastrointestinal
HES	Hospital Episode Statistics
HF	heart failure
HSR	Health Services Research
IBS	irritable bowel syndrome
IPD	individual patient data
IQR	inter-quartile range
LDL-C	low-density lipoprotein cholesterol
LLD	lipid-lowering drug
MEMO	Medicines Monitoring Unit
MI	myocardial infarction
NICE	National Institute for Health and Clinical Excellence
NNT	number-needed-to-treat
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
PTCA	percutaneous transluminal coronary angioplasty
RA	rheumatoid arthritis
RCT	randomised controlled trial
RGF	Research Governance Framework
RR	relative risk
SASH	Somerset and Avon Survey of Health
SD	standard deviation
SE	standard error
VAS	visual analogue scale

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

The exclusion from trials of people likely to be in need of or to benefit from an intervention could compromise the trials' generalisability. We investigated the exclusion of women, older people and minority ethnic groups, focusing on two drug exemplars, statins and non-steroidal anti-inflammatory drugs (NSAIDs).

Objectives

- Scope the social, legal and ethical contexts of trial exclusion, comparing the UK with the USA.
- Document disparities between people included in trials, those using the drugs and those in need of the treatment.
- Project the effects of exclusion on the generalisability of trials, referring to effectiveness (statins) and adverse effects (NSAIDs).
- Develop a theoretical model for the causes and effects of exclusions.

Methods

Scoping

We reviewed literature on the exclusion of women, older people and ethnic minorities in healthcare research and held three workshops with stakeholders.

Trials

We analysed 27 randomised controlled trials (RCTs) of statins use for secondary prevention of coronary heart disease (CHD), lasting at least 6 months (up to August 2001). We analysed a stratified sample of 25 NSAIDs trials for pain in osteoarthritis (OA) (up to 1998, prior to the introduction of coxibs).

Cohorts

Using a Scottish cohort with record-linkage [Medicines Monitoring Unit (Dundee) (MEMO)], we profiled 3188 people needing secondary prevention for CHD (1993–1996), ascertaining the independent effects of statins, and 131,410 people dispensed NSAIDs (1989–1996), examining adverse effects.

Use and need

To profile the need for secondary prevention of CHD in England we accessed routine data sources including Hospital Episode Statistics (HES). To estimate usage we consulted published surveys. For potential need and usage of NSAIDs in OA we accessed the Somerset and Avon Survey of Health (SASH) 1996–97 and published data.

Disparities

For both drugs, we compared the socio-demographic profiles of trial samples, the population in potential need and those on treatment.

Epidemiological/statistical assumptions

We produced an evidence synthesis to clarify the effects of statins on women and older people. We modelled the relationship of absolute effectiveness outcomes (e.g. numbers needed to treat) with underlying risk levels of disease events, examining the likely effects of trial exclusions.

Results

Scoping

In the USA, the discourse has expanded from protecting the vulnerable to include justice and the equitable access of different groups to trials. Appropriate representation of women and ethnic minorities in publicly funded trials is required by legislation. Guidelines recommend appropriate inclusion by age. In the UK, the debate is more limited, and equity and inclusivity in research are not formally promoted.

Trials

Statins

The average age of trial participants was 58.5 years; only 16.3% were women. Statins reduced cardiovascular disease (CVD) incidence by about 25% in both men and women. Older people up to 75 years of age also benefited. Meta-analysis and two landmark trials, containing large proportions of women and older people (published after 2001), confirmed these results.

NSAIDs
The average age of trial participants was 61.9 years and women were well represented (68.5%). Gastrointestinal (GI) adverse events were commonly reported, but renal side-effects were not. Outcomes were seldom reported according to socio-demographic group.

For both drugs, USA trials were more inclusive than UK/European trials. Ethnicity was not well reported for either drug.

Cohorts
Statins
Some 23% of the cohort were treated with statins. Statins users were younger than non-statins users (but no more likely to be male) and had superior outcomes.

NSAIDs
High current exposure to NSAIDs elevated the risk of GI side-effects by about 50% versus no current exposure and renal impairment risk by nearly 140%. Side-effect risk increased with age; being female diminished risk.

Use and need
Statins
Approximately 537,000 incident cases of CVD would qualify for statins use in England each year. Women constitute 45% of this population with need, two-thirds of whom are aged 65 years or over. Need varies by ethnic group. No sex bias in prescribing was detected, but use was commoner in younger people.

NSAIDs
6.3% of adults aged 35+ years reported hip and/or knee pain associated with OA; 3.9% of adults used prescribed analgesics for this and they were more likely to be women and to be >65 years old.

Disparities
Statins
Women formed almost half of the 'with need' and 'on treatment' populations, but were markedly under-represented in trials. Those aged 65+ years formed nearly two-thirds of the 'with need' population, but only one-fifth of trial samples, and were less likely to be treated than younger subjects.

NSAIDs
Women formed similar proportions (two-thirds) of trial samples, and of the 'with need' and 'on treatment' populations. People aged 65+ years formed about three-fifths of the 'on treatment' population, but were under-represented in trials. Association of side-effects with socio-demographic factors was revealed in cohort data but not in trials.

Epidemiological/statistical assumptions
Meta-analysis might overcome problems of low inclusion for the assessment of relative effectiveness, but the assessment of side-effects in different groups would require massive trials. Measures of absolute effectiveness are vital for the analyses of benefit and harm and cost-effectiveness. Such measurements, involving underlying risk levels, will be severely biased if different population groups are not adequately represented.

Main conclusions

The issue of exclusion from trials of women, older people and ethnic minorities has been relatively neglected in the UK research community, and there is confusion about diversity issues. Under-representation occurs, but in drug trials at least this may not always affect the external validity of relative effect estimates. However, measures of absolute effectiveness, absolute harm and cost-effectiveness are associated with underlying risk levels in different socio-demographic groups. Under-representation will therefore bias absolute effect estimates. The complexity of the issues made development of a theoretical model impossible.

Recommendations for future research

The following areas are suggested for future research:

- Multi-disciplinary assessment of realistic options for trialists to address the issue of exclusions.
- Clarification of the use of ethnic categories in health research and of the implications of the different dimensions of ageing and sex/gender.
- Identification of barriers and facilitators to the involvement of different population groups in research.
- Further investigation of the susceptibility of older men to NSAID adverse events.
- Development of a 'register of registries and databases' and exploration of how linked health information systems in the UK could be improved.

Chapter 1
Introduction

The central problem

The commissioning brief posed the question, 'What are the effects on the external validity of clinical trials of socio-demographic exclusion criteria?'.[1] The contention was that there is a predominance of middle-aged white men in trial samples, and as a result the efficacy or effectiveness of treatments in such trials might be different from those that would be experienced by, for example, women, older people or ethnic minorities. By way of introduction, we provide here further background to the nature of the problem posed and our interpretation of it, as the latter drove the research undertaken in our project.

Interventions available in healthcare are increasing in number, cost and complexity.[2] Clinical trials are the main way of assessing whether a new intervention is effective or not and how it compares with other options, including existing therapies. The best evidence comes from randomised controlled trials (RCTs) because randomisation avoids selection of who does and does not receive treatment and reduces the risk of confounding effects.[3] Evidence-based medicine uses findings from RCTs to produce systematic reviews and meta-analyses of all data available on a particular intervention, so that clear conclusions about its efficacy or effectiveness can be drawn and disseminated.[4] The results of these systematic reviews and meta-analyses frequently appear in the Cochrane Database of Systematic Reviews and they are also used to contribute to guidelines, such as those coming from the National Institute for Health and Clinical Excellence (NICE), which advise healthcare providers when and how to use an intervention.

Much attention has been paid to the internal validity of RCTs and to sources of bias that might arise from problems that threaten their internal validity.[5] Less attention has been paid to the important question of the external validity (or generalisability) of trials.[6,7] One major factor that might affect external validity is the exclusion from a trial of the type of people most likely to be in need of treatment from the intervention being tested. For example, if an intervention were designed to treat a condition that is highly prevalent in elderly women, but all the data to support its efficacy came from trials that only included young men, one would legitimately worry that, in clinical practice, elderly women might not respond as expected. One of many possible reasons for such a concern might be that the drug would be metabolised differently in elderly women (because of compromised renal or hepatic function) than it would be in young men.

The wider issues

However, to extend the above example, there might be equal or even greater concern about differential toxicity in the two groups (elderly women versus young men), for it is well known that some drugs are more likely to produce adverse effects in older than in younger people.[8–10] For this reason, we broadened the scope of our project to include severe adverse effects in additional to efficacy. The generalisability of a clinical trial might also be affected if certain socio-demographic groups are markedly under-represented in the sample, even if they are not completely excluded. We therefore decided to pay particular attention to the varying levels of inclusion of socio-demographic groups in trials, as an integral part of our research.

The commissioning brief mentioned three groups of people (older people, women and ethnic minorities) to whom the work should apply, in the context of the UK's NHS. Accordingly, we undertook work to examine each of the three groups mentioned. However, it is clear that there is the potential for complex interactions between these groups. For example, there are more women than men in the older age group. Similarly, some aspects of ethnicity might affect the willingness of groups of a particular age or sex to take part in trials. Further complexity is introduced by the relationships between age and co-morbidity, sex (i.e. the biological differences between men and women) and gender (i.e. the social differences between men and women) and ethnicity and race. These complexities assumed increasing importance and relevance as our work progressed, affecting the nature of the work undertaken, its outcomes, and this report.

The commissioning brief suggested that the major focus of the research should be on the effects of the exclusion of certain groups from trials. It stated, for example, that 'the reasons for (trial exclusions) may include the costs of running the trial as well as the wish to exclude patients with co-morbidity or those unlikely to accept or respond to experimental treatment'. Our initial reading of the literature suggested that only limited work had been done on either the nature of trial exclusions or the reasons why these exclusions took place. Because of this, we again broadened the range of the project, including a literature review and scoping work on the nature of such exclusions and the likely causes of them. We also decided that there was a need for an international perspective. Although the generalisability of trial findings to NHS patients is, rightly, the main concern in the UK, trials that are used to derive guidelines and recommendations come from all over the world. The USA is clearly the most dominant country in this regard, has recognised the existence of problems of exclusion from healthcare and trials by age, sex, gender or ethnicity for some time, and has introduced legislation to try to help avoid some of them. We therefore undertook work to contrast the situation in the UK and USA in the belief that this would throw valuable light on the subject.

The brief made it clear that the main methodological challenge of the work would be in assessing the effects of trial exclusions on the external validity of the data. We suggested the use of meta-regression and other evidence-synthesis techniques. The ideal method would be the analysis of individual patient data from RCTs. This method would only be suitable for a longer term project, however, as it would involve achieving collaboration between a number of international groups of trialists.

The final issue that we had to address when planning our work was the clinical areas in which to undertake it. Clearly, the exclusions problem could apply to some, any or all of the many thousands of different interventions available in the NHS. One could only find this out by examining each intervention and, clearly, this would be impractical. We decided to concentrate on two different exemplars which we thought might throw up contrasting issues, and in which we had appropriate background expertise, with access to the relevant literature and understanding of it. First, we selected statins (for reduction of blood cholesterol), where we predicted that older people, in particular older women, would be largely excluded from trials, in spite of their having a potential need for therapy.[11,12] Second, we selected non-steroidal anti-inflammatory drugs (NSAIDs) (for relief of musculoskeletal pain), where we predicted that exclusion of older women would have more relevance to the toxicity than the efficacy of the drugs.[13] We predicted that exclusion of ethnic minorities would be common to both types of intervention, but we were unable to predict potential causes or effects of any such exclusions that we might find.

Aim of this research

We aimed, therefore, to investigate the potential causes of the exclusion from clinical trials of three groups, namely women, older people and ethnic minorities, to map the actual levels at which these groups were represented in trials, and then to examine the effects on results of the exclusion of these groups in terms of specific information gaps between levels of treatment in clinical practice and need for treatment in the population. We also wanted to identify overlaps and interactions between these three groups. We decided to do this work through a mixture of primary and secondary research, employing both qualitative and quantitative techniques, and involving researchers from social science, epidemiology, Health Services Research (HSR), statistics and clinical medicine. We focused on the two treatments mentioned, namely statins and NSAIDs. Where feasible, we wanted to compare and contrast exclusions from trials in USA and UK settings.

Specific objectives

We had six pre-defined specific objectives:

1. **To explore the social, legal and ethical factors behind exclusion**. This exploration would take the form of a scoping, qualitative exercise to examine the conceptual and contextual background to trial inclusion/exclusion. There would be particular emphasis on the different socio-political and legal contexts in the USA and UK.
2. **To explore current practices of key stakeholders**. The literature would be examined and some interviews would be undertaken with trialists to ascertain their views on trial inclusion/exclusion. In addition, interdisciplinary workshops would be held relating to the three socio-demographic groups of interest. These workshops would take a

broad view of the setting of our central problem, allowing for presentation of research relating to gender, age and ethnic minority issues in public health, observational and diagnostic research, in addition to those in clinical trials.

3. **To map and quantify the extent to which the three socio-demographic groups (women, older people and ethnic minorities) are excluded from trials**. This would involve examination of a series of statins trials and a series of NSAIDs trials to ascertain inclusion/exclusion criteria, the level of representation of the three groups and also to ascertain the way treatment effects and adverse events are reported.
4. **To document any disparity between those included in the clinical trials, those receiving treatment in the 'real world' and those in need of treatment in the 'real world'**. This would be based on the comparison of data on people involved in the two series of trials with findings from the 'real world'. These findings would include survey and registry-derived data (including hospital activity data) recording people who were being prescribed statins and NSAIDs, and also epidemiological data describing people with an evident need for these drugs.
5. **To model the effects on external validity (generalisability) and on the evidence base of different levels of representation in trials**. We would employ various techniques, including meta-regression, to estimate the effects of socio-demographic exclusions on external validity (generalisability) and on the evidence base. We undertook to estimate the extent to which health researchers might make valid inferences about the effects of treatment for women, older people and ethnic groups if they generalised from trial data drawn from restricted groups of people.
6. **To develop a theoretical model for the social and biological causes and for the effects of trial exclusions**. This would be a synthesis of all the work in our study. We would develop an overview and understanding of the influences leading to exclusions in trials and of the potential consequences of restricting trial entry to people who are not representative of the community or who are not representative of those in need of treatment. This would be done in the hope that such a model might be valuable for the understanding and the study of other interventions not included in this research.

Structure of the report

The structure of this report largely follows the sequence of the six specific objectives described above. The penultimate chapter describes the broader field of trials, only a section of which could be investigated in our study. In the final chapter we summarise our work, present our conclusions and make recommendations for future research.

Chapter 2

The background: debates about equity and justice in medical research

Introduction

The past four decades have seen extensive debate in many countries about the ethics of medical research. In the period immediately following the promulgation of the Nuremberg Code[14] and the Helsinki Declaration,[15] concern was directed mainly at the avoidance of harm to actual and potential subjects.[16,17] However, the 1970s saw a gradual change of focus towards the rights of those who were excluded from participation. Hence the discourse expanded from one of protection alone to encompass a concern with equitable access. Although these debates were at their most intense in the USA, they have also influenced thinking in research communities in other parts of the world.

An introductory analysis of these ethical developments was undertaken as part of this project. Debates in the USA were explored through a qualitative scoping review of the relevant literature and of associated policy documents. The scoping review is a technique employed here to provide an overview of this field of research as a prelude to the more detailed investigations, which are reported in the succeeding chapters. This particular review involved both MEDLINE and hand searches of a range of medical and ethical databases. We supplemented a similar review for the UK with a series of workshops on age, gender and ethnicity in healthcare attended by key stakeholders involved in the funding and implementation of clinical trials and other forms of health research. In addition, interviews were conducted with five UK trialists. (The workshop discussants and details of the specific topics addressed are given in Appendix 1, where the names of the trialists interviewed are also given.) The aims of the workshops were threefold. First, they were themselves a source of data collection, since participants were able to express their own perceptions on a range of equity issues and these became part of the project team's understanding of current debates. Second, they provided a much-needed forum for moving these debates on in a situation where they have so far received relatively little attention. Third, they played an important role in disseminating the findings from our project, since the proceedings have been made available as separate publications. The interviews that were carried out with the five trialists were semi-structured and explored a wide range of issues relating to who would be included in particular trials and how differences between population groups would be interpreted in research analyses.

This introductory chapter provides an overview of the findings from these two reviews. It begins with a summary of USA developments and then explores the extent to which similar concerns have been addressed in the UK. The basic finding will be that issues of justice in medical research have received much less attention in the UK than in the USA, despite the probable existence of similar inequities relating to age, sex/gender and ethnicity in the design and implementation of clinical trials. The focus of this chapter will be on issues of 'equity' and not 'scientific generalisability', but the rest of the report will highlight some aspects of the interconnectedness of these two themes.

Justice in medical research: the USA experience

In the USA, traditional concerns about protecting the interests of vulnerable people were heightened by revelations of abuse during the 1960s and 1970s.[16,17] The vulnerability of older people was highlighted in 1963 with the discovery that physicians at the Jewish Chronic Disease Hospital in Brooklyn had injected live cancer cells into elderly debilitated patients without their proper consent. These concerns were exacerbated in the early 1970s by revelations about the infamous Tuskegee Syphilis Study. About 400 African American men were included without giving proper consent and many were left untreated even after antibiotics became available. It was in response to these revelations that the USA government formulated the first federal regulations to protect human research subjects in 1974.

Although these examples highlighted the exploitation of older people and those from ethnic minorities, concerns were also being expressed

about the situation of women as the subjects of medical studies. The thalidomide disaster in the late 1950s and also the DES (diethylstilbestrol, a synthetic oestrogen) cases that occurred a decade later, were not the result of participation in research. However, they were potent reminders of the potential hazards of medication for pregnant women and their children. These concerns were reinforced by publicity relating to the use of poor women as 'guinea pigs' in contraceptive trials. In response to these developments, women in general and pregnant women in particular were defined as a 'vulnerable group' and a decision was made by the Food and Drugs Administration (FDA) to exclude women of childbearing age from the early phases of USA drug trials.[18]

A new focus on inclusion

During the 1970s, policies therefore focused mainly on the protection of research subjects, but by the end of the decade there was also a growing concern about the rights of those who were unable to gain entry to clinical trials. The Belmont Report of 1978[19] highlighted the potential benefits of more diversity in study populations both for the individuals concerned and for the population groups from which they came. It also emphasised the need to respect the autonomy of all legally competent individuals in making decisions about whether of not to participate in research. This new approach laid the foundations for a shift away from paternalism towards a focus on greater justice in access to trials.

Wider social and political developments reinforced this process with the emergence of HIV/AIDS, raising new questions about access to experimental drugs. In the initial stages of the epidemic, the therapeutic options available to infected individuals were extremely limited. As a result, many looked towards the next drug as their only hope and entry into clinical trials was eagerly sought, but the old protectionist model often placed obstacles in their way. AIDS campaigners therefore argued for such controls to be lifted and in 1987 the FDA issued regulations making access to new drugs easier in the context of serious and life-threatening illness.

While AIDS activists were demanding the right to make their own judgements about potential risk, groups of women and their advocates began to look at medical research from a feminist perspective.[19,20] They argued that the male domination of priority setting meant that some problems specific to women were not receiving sufficient funding and campaigned for more support for research into breast cancer in particular. Furthermore, the concerns of the activists went beyond the determination of research priorities. They were also critical of the inadequate representation of women in clinical trials of drugs for the treatment of health problems relevant to both sexes.

In the early 1990s, evidence had begun to emerge that men were included much more often than women as the subjects of medical research.[21] As a result, women were less likely than men to gain entry into trials that might be to their benefit. This was certainly true for HIV-infected women, who found it much harder than men to achieve access to new drugs.[22] A great deal of medical knowledge was therefore based on findings derived mainly from the experiences of men and its applicability to women was less certain. Hence women were also disadvantaged as a group. In the case of coronary heart disease (CHD), for example, some of the most important clinical trials and epidemiological studies of the past decade had involved either all-male or predominantly male samples.[23] There was therefore a strong suggestion that the treatment received by women with CHD (and other health problems) was likely to be less effective than that offered to men and this raised important equity concerns. Latterly, a dissenting voice in the debate has been provided by Bartlett,[24,25] who has controversially argued that any numerical disadvantage to women has been confined to the field of cardiovascular medicine.

Very similar issues were raised over the same period by those concerned with the rights of ethnic minorities in the USA.[26] Just as health problems of particular relevance to women had, it was claimed, been given low priority, so had those predominantly affecting African Americans and other minority ethnic groups. At the same time, evidence was emerging that many studies of health problems affecting all groups were based on the inclusion of white people in greater proportions than were found in the general population. Again, this raised important questions about the applicability of research findings to all potential patients.

Developing a strategy for distributive justice

In response to these concerns, the USA government introduced a number of new

measures. These culminated in the creation of the Office of Research on Women's Health in 1992 and in the NIH Revitalization Act of 1993.[27,28] The latter included Guidelines on the Inclusion of Women and Minorities as Subjects of Clinical Research and all applications for federal funding now have to show that these groups are represented in the research design in appropriate numbers. Older people were not included in the 1993 Act, but FDA guidelines have highlighted the need for studies to reflect the age distribution of the population in which drugs are likely to be used.[29,30]

The last decade has therefore seen the implementation of a range of strategies designed to promote greater justice in medical research in the USA. Protectionist concerns have remained firmly on the agenda with the development of more proactive and creative ways of ensuring informed consent.[16] This has been accompanied, however, by policies to achieve a more equitable distribution of the benefits as well as the burdens of research. It is widely accepted that individuals may gain from access to new treatments while particular population groups will be better served if medical knowledge is based on a clearer understanding of their needs. Hence a range of stakeholders including regulatory bodies, funders, Institutional Review Boards (ethics committees) and individual scientists are now required to pay attention to equity issues in the development, implementation and evaluation of research projects.

Of course, distributive justice will not be easily achieved and the USA experience has highlighted many of the inevitable tensions. For example, the requirement to include a large number of subjects from different groups may lead to studies becoming unacceptably expensive. Attempts to monitor the impact of recent policies show that there is much more to be done,[16,31–34] but it is also clear that there has been a radical shift in the culture of USA medical research towards greater inclusivity. Similar trends are evident in a number of other countries including Canada, Australia and South Africa. However, there is little sign of similar trends in the UK, as we shall see in what follows.

Justice in medical research: the UK experience

The review of UK policies revealed, in comparative terms, a lack of awareness of broader equity issues in the conduct of health research in general. The main focus of research ethics has continued to be a paternalist one. Debates have been low key and there has been little or no political activism of the kind found in the USA. Few of the arguments relating to distributive justice have entered the public policy arena and a review of both UK and European guidelines for the implementation of clinical trials showed little awareness of equity issues. (An annotated list of policy documents and websites is given in Appendix 2.)

A recent Health Technology Assessment (HTA) programme publication reviewed current debates about inclusion and exclusion, but referred only to technical questions concerning validity and representativeness.[35] The philosophical or ethical implications of these issues were entirely ignored. Issues of justice are similarly absent from the guidelines for research ethics committees, though the new Research Governance Framework (RGF) for the UK does talk in very broad terms about the need to ensure that the body of research evidence 'reflects the diversity of the population'. The framework offers no practical suggestions on how this might be achieved or on the methodological problems involved, however.

Not surprisingly, this lack of interest at the policy level is reflected in a sparsity of empirical studies exploring the representation of different population groups as research subjects. Few investigators have examined the representativeness of studies carried out in the UK separately from those done elsewhere in the world, but the available evidence suggests that here too, there are problems relating to equity of access. In the following sections we explore the implications of this for the main groups affected: older people, women and people from ethnic minorities. As we shall see, concerns have been raised about the representation of all these groups in clinical trials. There are also much wider issues at stake about how these groups are defined and how differences between them and the wider population are measured and their health implications assessed.

Age as a variable in clinical trials: the UK experience

The exclusion of older people from medical research has received considerable attention in recent years.[36–38] Indeed, it is probably in this group that evidence of unequal access to UK studies is strongest. A review of major British

medical journals between June 1996 and June 1997 found that one-third of the original research papers excluded elderly people without offering any justification.[39] Similarly, a review of all studies submitted to a Welsh research ethics committee during the first seven months of 1999 found that half of those that were potentially of relevance to older people had an upper age limit which appeared to have no justification.[40] Neither local nor multi-centre research ethics committees had challenged these restrictions.

In discussing age bias, a number of commentators have focused on cardiology research in particular. People over the age of 65 years and especially those older than 75 years, have been found to be significantly under-represented in studies carried out in the UK and the USA.[39,41] Older women are especially likely to be excluded.[11] This is clearly problematic given the relatively greater representation of older people in general and older women in particular in the population of cardiology patients. A major trial of bisoprolol had an upper age limit of 80 years. However, the mean age of patients in the trial was 61 years. As the authors themselves pointed out, there is therefore inadequate information about the effects of this treatment in older patients.[42]

The reasons given by researchers for the low levels of representation of older people in trials are confusing and sometimes contradictory. The first set of arguments relates to their deliberate exclusion on what are called 'scientific grounds'. Central to this argument is the claim that older people are more likely to experience 'co-morbidity'. That is, that they are more likely to have another pre-existing health problem, which may confuse the results. They are also said to be more likely to die prematurely and therefore to dilute the treatment effects and/or to lengthen the trial. These arguments appear to assume particular importance when trials are commercially funded.[43] However, those arguing for the rights of older people have pointed out that many are perfectly healthy and do not have a high risk of dying before the study is completed. Hence age is not in itself a valid reason for exclusion.

The second set of arguments used to exclude older people suggest that they are unable to comply with outcome measures or (less often) that they cannot give appropriate consent. Again, this may be true of some people over (and some under) the selected age, but it is by no means true of all. Of course, the inclusion in trials of individuals who are physically or mentally frail will pose serious challenges for researchers. It may be difficult to gain proper informed consent to a complex trial where the terms used may not be properly understood. Also, there may also be serious obstacles to follow up for those with limited mobility or impaired cognition, but this should not lead to an *a priori* decision to exclude all those over a certain age.[11] Nor should it be allowed to interfere with the rights of individuals who are eligible to participate, but are excluded at the recruitment stage for inappropriate reasons associated with their age.

The failure to include older people in studies in proportion to their likely need for treatment raises serious equity issues. Utilisation of health services increases with age. People aged over 65 years comprise about 14% of the population in the UK yet they consume nearly one-third of all drugs.[36,44,45] There is therefore a continuing lack of 'fit' between study samples and likely consumers. This was highlighted by a recent survey showing that only 10% of women in UK trials for adjuvant therapy for breast cancer were over 70 years old even though this age group make up about half of those with the disease.[46]

There is already evidence that ageing is associated with an increase in the frequency of adverse drug reactions, and other age differences are likely to emerge if studies are designed appropriately.[10] Under these circumstances, their almost routine exclusion from much medical research is hard to justify either clinically or ethically.[17] Instead, these patterns of exclusion need to be seen as part of a bigger picture with low priority given to most conditions of old age such as incontinence or strokes and to geriatric medicine as a whole. This has led many commentators to argue that it is not 'good science' but discrimination against the old, which plays a significant part in sustaining these differential opportunities to benefit from research.[40,43,47]

Adding to these scientific and ethical inconsistencies is a conceptual confusion about the distinctions between chronological, biological and social age. Chronological age is frequently used as a proxy for other conditions such as cognitive impairment. If such biological conditions are important criteria for exclusion (or inclusion), then they need to be properly defined and independently measured. Much greater clarity is also needed about the distinction between biological and social ageing. The health of individuals may be affected both by the

physiological processes of ageing itself (biological ageing) and also by changes in their social and material circumstances (social ageing). For example, older people may be treated with less respect and may have access to fewer resources than they had in earlier stages of their lives. Unless these separate strands of chronological, biological and social ageing are properly understood, researchers will be limited in their capacity to make sense of any observed differences between age groups.

Sex and gender as variables in clinical trials in the UK

The failure to include older people in trials is clearly of particular relevance to women, since they make up the majority of elderly people in the UK. We know very little about their representation in studies at other stages of the life cycle. However, a recent survey indicates that the situation may be at least as unbalanced as it is in the USA. A survey of statins trials carried out between 1990 and 1999 found that they were highly skewed towards men.[48] In trials of statins for secondary prevention, the average female participation rate was only 23% whereas in the primary prevention category the rate was as low as 10%. This led the authors to comment that there is very little evidence for the benefits (or otherwise) of statins therapy for women of any age.

There are therefore reasons for concern about the relevance of UK research findings for women just as there are for older people. The reasons for these gender inequalities in representation are again confusing and often contradictory. On the one hand the failure to include women often seems to rest on the unexamined assumption that they are similar enough to men to make it unnecessary to look at them separately. On the other hand, exclusion is also justified by some on the grounds of potential pregnancy and what are seen as the vagaries of menstruation. Hence women are sometimes seen as enough like men to warrant safe exclusion while also being represented as too different to be safely included. Yet women of all ages and states of fertility are likely to be offered treatment based on studies in which they have been under-represented.

This lack of clarity about the inclusion/exclusion of women in clinical research reflects a basic underlying confusion about the implications of 'maleness' and 'femaleness' for human health. In particular, there is still a fundamental misunderstanding about the meaning of the terms 'sex' and 'gender'.[49] Many researchers still use these concepts interchangeably, assuming gender to be a more politically correct term for sex. When used correctly, however, the term 'sex' refers to biological differences between women and men whereas the term 'gender' refers to social differences. In the USA, the implications of this distinction for biomedical research have been widely debated.[50,51] In the UK, meanwhile, these issues remain largely unexplored.

In the case of heart disease, for instance, we know that there are biological or sex differences between women and men in age of onset and probably also in prognosis, but we also know that there are social or gender differences in the way that women and men choose to respond to signs and symptoms. Women may take longer to get treatment, for instance, because they see heart disease as a 'male' problem. Once women and men enter the healthcare system, it is also clear that 'gendered' ways of thinking mean that doctors sometimes treat women and men differently. We know, for example, that women tend to receive fewer investigations than men even if their clinical condition is very similar.[52] Hence any observed differences in outcome between women and men may be due either to biological or to social factors (or to a combination of both). Failure to recognise this may lead to the drawing of inaccurate conclusions.

Strategies for the promotion of sex and gender equity in medical research therefore need to move beyond policies for the inclusion or exclusion of female participants. They also need to address more fundamental issues concerning the definition, measurement and interpretation of differences between women and men and the implications of those differences for health and healthcare.

Ethnicity as a variable in clinical trials: the UK experience

Alongside concerns about age and gender representation in UK clinical trials, the absence of people from ethnic minorities has also been noted. As yet there is little definitive evidence about the extent of such perceived inequalities. However, a recent study explored the representation of ethnic minorities in cohort studies of cardiovascular disease (CVD) carried out in the USA and Europe.[53]

Studies in the UK were not separately identified but in Europe as a whole the results were very striking. Out of 34 studies reviewed, 25 gave no indication at all of ethnicity or race in the sample. In three cases the study population was explicitly Caucasian or white, in four cases the sample was taken from a location where minorities were likely to be under-represented, in two cases the study was explicitly designed to compare European origin ethnic groups and in only two were other ethnic/racial minority groups selected out for separate analysis.

The reasons for this failure to include ethnic minority populations in clinical trials are again complex and relatively unexplored. However, it is significant that so many researchers felt no need to comment at all on the ethnic composition of the sample. This seems to suggest a widespread failure to recognise the possible implications of ethnicity for the development of an appropriate knowledge base.[54,55] Given the attention paid to ethnic diversity in the wider debate about inequalities in health in the UK, this is a surprising gap. There is a growing volume of evidence relating to variations between ethnic groups both in health status and in the utilisation of services.[56,57] Nonetheless, this does not appear to have been translated into biomedical research and as a result most trialists fail to take issues of ethnicity seriously.

In addition to what could be seen as this benign neglect of minority ethnic populations, many researchers also make explicit decisions to exclude those whose first language is not English. The reasons given for the use of linguistic exclusion criteria will usually be the cost of interpreting and the difficulty of getting informed consent, but they also reflect the (understandable) desire of many trialists to acquire a homogeneous sample with as little difficulty as possible, whatever implications this may have for the representativeness of the sample.

Even if they are not formally excluded from a trial, potential ethnic minority participants may also face obstacles at the recruitment stage. A number of these were identified in a recent survey carried out in the Yorkshire/Humber Region. In the first study of its kind in the UK, health professionals, lay people and trial participants from various South Asian backgrounds were interviewed about the barriers they perceived to minority involvement in research.[58] The health professionals commented that lack of resources and of culturally similar staff, geographical and language barriers and fear of the unknown could all limit the recruitment of minorities. Many also said they had not been aware of ethnic under-representation or its significance. South Asian interviewees, on the other hand, talked about religious and cultural issues that were not taken seriously by those involved in the recruitment process. They also highlighted the fact that potential ethnic minority participants might decline to take part because they did not feel able to trust the researchers.

Pressure is beginning to emerge for UK studies to include ethnic minority populations in numbers large enough to allow for robust subgroup analysis.[53] There have also been calls for specially designed studies of health problems in specific population groups, but the inclusion of more people from ethnic minorities in clinical trials will not be enough. More attention will also need to be paid to the conceptual and methodological problems involved in making sense of 'race' and 'ethnicity' in health research.[54–57,59–63]

As we saw in the case of age and sex/gender, there is a need to be much clearer about the distinction between the biological and the social, between the biological category of race and the social category of ethnicity. There is now wide agreement that the term 'race' should be avoided since it adds little to the evidence base of medicine and may be used to stigmatise particular communities. Different population groups do experience different health problems and biology is sometimes relevant in explaining these. Sickle cell anaemia, for example, provides an obvious illustration of this since it is concentrated mainly in African and Caribbean groups. However, the concept of 'race' does not help us to understand how this works.

The social concept of ethnicity, on the other hand, can be of value in helping to illuminate the ways in which the material and cultural circumstances of minority groups affect both their health status and their healthcare needs. However, the use of the term is always fraught with difficulty because of the fluid and changeable nature of ethnicity in both individuals and populations. People have identities and cultural locations derived from the origins of their parents and also from their own experiences over the life cycle. Similarly, ethnic groups themselves will be reshaped and redefined over time and space. This is not always reflected in biomedical research, where criteria for allocation of a particular ethnicity are too often poorly defined and its implications understood in social rather then biological terms.

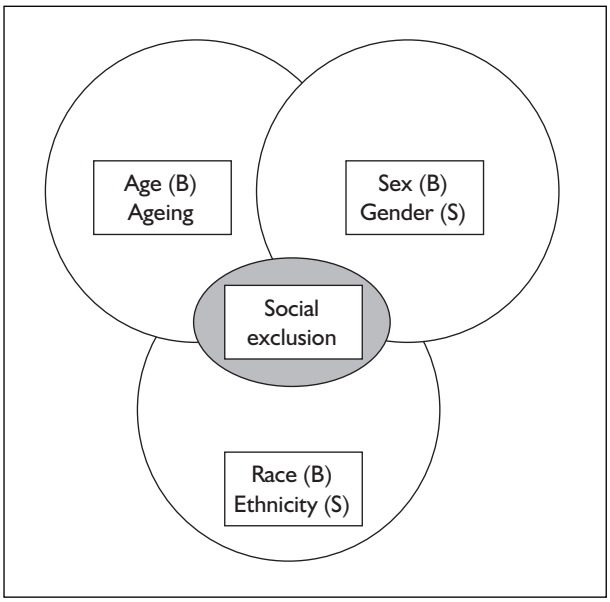


FIGURE 1 *The three socio-demographic domains under consideration in this report are age, sex and ethnicity. In each case there is a biological (B) and a social (S) dimension to the domain. In addition, there are complex interactions and overlaps between each domain, with many people collocating in a section of the society, which is relatively excluded.*

People from ethnic minorities, older people and women are all more likely to be economically disadvantaged and socially excluded than middle-aged men. Therefore, there are complex interactions between each of these aspects of socio-demography, as shown in *Figure 1*.

Conclusions

We concluded that UK debates about justice in healthcare research remain limited by comparison with those in the USA. However, it has also been shown that there are reasons to be concerned about the representativeness of UK trials in relation to age, sex/gender and ethnicity. More discussion is needed about the implications of these inequalities for distributional justice and also for the generalisability of research findings across the UK population. The remainder of this report will explore these issues further in detail through investigation of trials of statins and NSAIDs and the need for and usage of these drugs in the 'real world'.

Summary: the background – debates about equity and justice in medical research

- We conducted a scoping study, covering the literature on the ethical dimension of the inclusion of women, older people and ethnic minorities in healthcare research.
- We compared the debates in the USA and the UK, supplementing the UK review with material from stakeholder workshops and interviews with trialists.
- In the USA the discourse has developed from one of 'protectionism' alone to encompass notions of 'distributive justice' and of equitable access to clinical trials.
- The appropriate representation of women and ethnic minorities in publicly funded trials is required by legislation in the USA.
- The US FDA has issued guidelines recommending that studies reflect the age distribution of the population in which the drugs are eventually likely to be used.
- UK debates about justice in health care research remain limited by comparison with those in the USA.
- The Research Governance Frameworks for the home nations within the UK refer to the diversity of populations, but offer no practical guidance or legislative support to promote the inclusion of different socio-demographic groups.
- There are reasons to be concerned about the representativeness of UK trials in relation to age, sex/gender and ethnicity.
- More discussion is needed about the implications of these inequalities for distributional justice and for the generalisability of research findings across the UK population.

Chapter 3

Mapping trial participants and trial outcomes: statins

Statins trials: background and objectives

Statins were designed to lower total cholesterol and low-density lipoprotein cholesterol in the blood by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis, and are prescribed for prevention of cardiovascular events.[64] Our main objectives were: to identify randomised statins trials; to document the socio-demographic characteristics of their samples and investigate possible external influences on inclusion levels for women, older people and ethnic minorities; and to ascertain the outcomes of the secondary prevention trials, identifying any results specific to women, older people and ethnic groups.

Statins trials: methods

We examined statins trials in two stages. In the first stage, we examined a complete series of randomised statins trials (indicated as 'all statins trials'), paying particular attention to possible external influences on inclusion levels. In the second stage, we examined a subset of this series, which consisted of trials for secondary prevention (indicated as 'statins secondary prevention' trials), because these were relatively numerous. Further details of methods for the second stage are given below.

To identify trials for the 'all statins trials' series, we conducted MEDLINE searches up to 1 August 2001 for randomised trials of statins in adults with a minimum treatment duration of 6 months (or 26 weeks), which reported lipid changes or stenosis change or cardiovascular events. We checked references in trial reports and relevant reviews and considered studies irrespective of their publication status or language. The search up to the beginning of November 1997 was undertaken as part of an earlier review of the efficacy of statins.[64] This search was then repeated to cover the period up to the end of our time frame, namely 1 August 2001. The search strategy is given in Appendix 3. We also took note of all reports of large statins RCTs, which came into the public domain after 1 August and up to the end of 2002. Although these trials were published too late to be included in the series, we refer to them as additional, important sources of evidence.

To be eligible, trials had to compare a statin with a non-statin drug, or with an inactive control or with 'usual care'. Adjuvant treatment with one additional drug if a patient developed excessively high lipids during the trial was deemed acceptable. We included factorial trials if appropriate data could be derived. Trials in which all patients had renal failure or diabetes at randomisation were not eligible. For clarity, we drew upon only one treatment comparison (e.g. statins arm versus placebo arm) per trial, taking the comparison first reported. In our results and summary, we refer to the comparison of interest as the 'trial'. If necessary, we approximated the mean age of all patients in a trial from any available data reported, such as mean ages for the statins arm and for the placebo arm.

We extracted trial characteristics (such as source of funding, location of research, inclusion and exclusion criteria) and patient characteristics (such as numbers, percentage women, ethnic details). We classified as 'secondary prevention' trials studies in which all patients had prior experience of one or more of the following conditions: myocardial infarction (MI), stable or unstable angina, cerebrovascular event, significant coronary artery stenosis or requirement of a heart transplant.

We classified as 'primary prevention' studies in which patients had evidently not already experienced any of these conditions at the outset of the trial. With regard to possible external influences on trials, we coded trials to 'USA' if all or some of the patients were located in the USA. We also coded trials according to whether support had been provided by the pharmaceutical industry. There was a distinct group of trials in which coronary or carotid artery stenosis was measured, so we coded these trials to 'angiographic'. Data were extracted by one researcher, with extraction duplicated by a

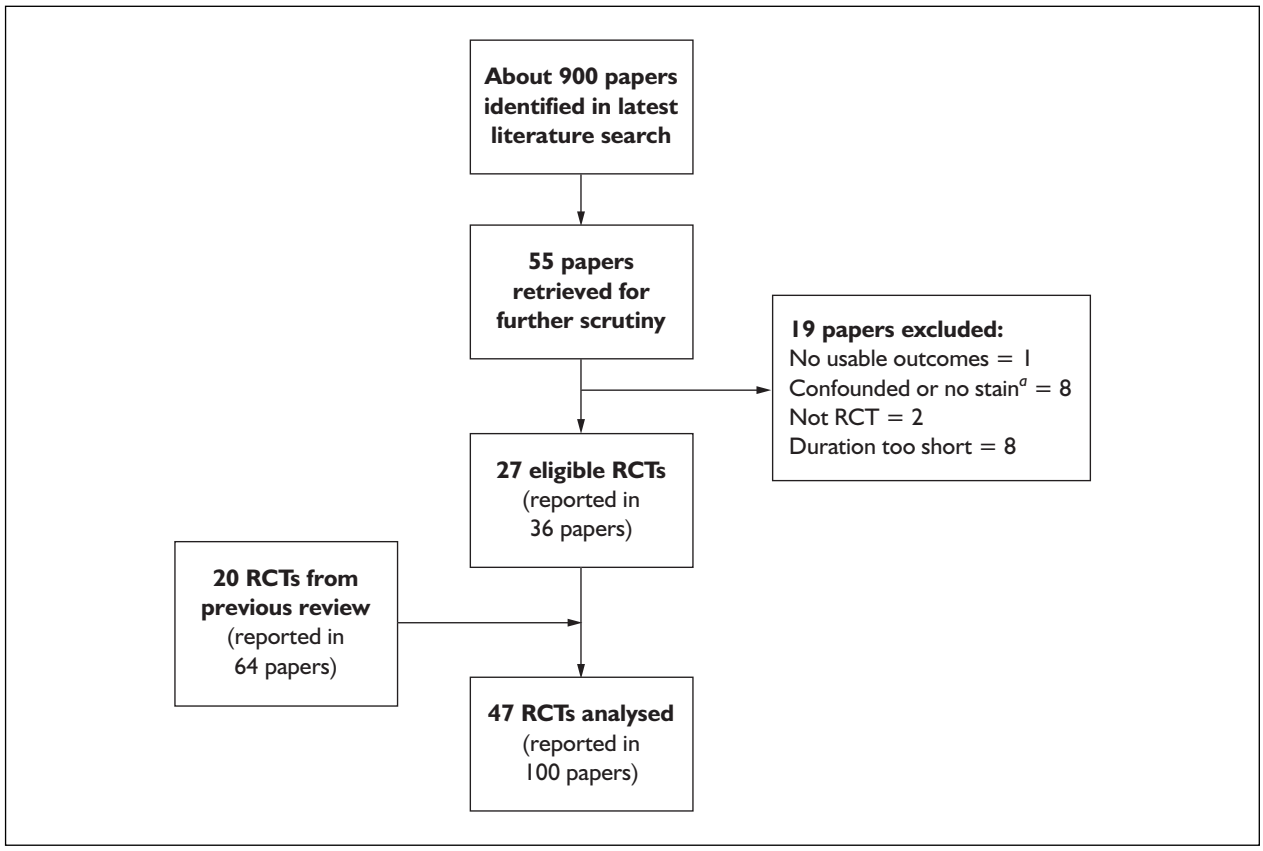


FIGURE 2 *Flowchart of stages of identifying eligible statins RCTs.* [a] *'Confounded' includes trials with statins as a study drug in both arms and trials in which more than one lipid reducer was used as rescue medication, adjuvant to a statin.*

colleague for key variables. Analysis was in STATA 7, using Fisher's exact test and the Kruskal–Wallis test. We report p-values ≤ 0.05.

All statins trials: results of literature search

All statins trials: results. Trial characteristics

In total, 47 RCTs, all published in the period 1990 to 2001 inclusive were eligible (*Figure 2*). The main characteristics of these 47 trials[65–165] are summarised in *Table 1*. Three large RCTs were published in 2002 and are described below. Papers scrutinised and excluded are described in Appendix 4.[166–183] The total number of patients in the 47 RCTs was 50,245, the median being 270. The mean follow-up period was 2 years. The statins involved were pravastatin (22 trials), lovastatin (12), simvastatin (nine), fluvastatin (three) and atorvastatin (one). We coded six studies to primary prevention, 29 to secondary prevention, nine to 'mixed' primary and secondary prevention and three studies did not give sufficient information for coding.

Eight trials (17%) reported complete exclusion of women from their samples and the median percentage of women included in the series of trials was only 19% [inter-quartile range (IQR) 12–30%]. Whereas 14 trials reported separate outcome information for women, only seven of these reported cardiovascular event data, often in a superficial way; only two trials distinguished between men and women in reporting adverse events. In all, 31 trials reported setting a definite upper limit for age, the median being 70 years, but 11 of the remaining trials were equivocal about this criterion. The percentage of people aged 65+ years was infrequently reported (13 trials), the median percentage being zero. Eleven trials reported outcome information by age group, although this was often minimal. Only eight trials (17%) reported the ethnic minority proportion in their respective samples.

All statins trials: results. Possible influences on trial characteristics

As *Table 2* shows, USA patients were involved in 17 trials. In comparison with non-USA trials, USA trials included a higher proportion of women (22.7% vs 16.5%), and had an older median age

TABLE 1 *Main characteristics of the 47 RCTs of statins in the series*

Refs	Prevention category	Short trial name	Year of publication[b]	Men (no.)[c]	Women (no.)[c]	Women (%)	Mean age (years)[d]	Any USA[e]	Solely pharmaceutical[e]	Angiography[e]
65, 66	Primary	CAIUS	1996	162	143	46.9	55			Yes
67	Primary	BAK	1998	107	0	0	55		Yes	
68–72	Primary	AFCAPS/TEXCAPS[a]	1998	5608	997	15.1	58.7	Yes	Yes	
73	Primary	Dangas	1999	15	47	75.8	62.2	Yes		
74	Primary	Su	2000	28	12	30	62.5			
75	Primary	Duffy	2001	5	9	64.3	29.1			
76	Secondary	FATS	1990	74	0	0	47.5	Yes		Yes
77	Secondary	Sahni	1991	110	47	29.9	60.3	Yes		Yes
78, 79	Secondary	MARS	1993	247	23	8.5	58	Yes		Yes
80–91	Secondary	4S[a]	1994	3617	827	18.6	58.6		Yes	
92–94	Secondary	LRT	1994	289	115	28.5	62	Yes	Yes	Yes
95–98	Secondary	ACAPS	1994	474	445	48.4	62	Yes		Yes
99–101	Secondary	CCAIT	1994	269	62	18.7	53		Yes	Yes
102, 103	Secondary	MAAS	1994	336	45	11.8	55.3		Yes	Yes
104	Secondary	Kobashigawa	1995	75	22	22.7	52	Yes	Yes	Yes
105–107	Secondary	PLAC-II	1995	129	22	14.6	62.6	Yes		Yes
108–110	Secondary	REGRESS	1995	884	0	0	56.2		Yes	Yes
111, 112	Secondary	PLAC-I	1995	316	92	22.5	57	Yes	Yes	Yes
113, 118	Secondary	CARE[a]	1996	3577	582	14.0	59	Yes	Yes	
119	Secondary	CIS	1997	205	0	0	49.6		Yes	Yes
120	Secondary	Wenke	1997	64	8	11.1	47.9			Yes
121	Secondary	Andrews	1997	28	12	30	67	Yes		
122	Secondary	Takagi	1997	25	0	0	56			Yes
123	Secondary	PREDICT	1997	582	113	16.3	58.4		Yes	Yes
124–126	Secondary	LCAS	1997	349	80	18.6	58.8	Yes		Yes
127	Secondary	CARS	1997	65	15	18.8	64			Yes
128–131	Secondary	LIPID[a]	1998	7498	1516	16.8	62			
132	Secondary	LISA	1999	225	140	38.4	59.8			Yes
133	Secondary	CLAPT	1999	226	0	0	53.9		Yes	Yes
134, 135	Secondary	FLARE	1999	688	146	17.5	60.5		Yes	Yes
136	Secondary	CARATS	2000	51	9	15	55	Yes	Yes	Yes
137, 138	Secondary	SCAT	2000	205	25	10.9	61			Yes
139, 140	Secondary	GISSI-P[a]	2000	3684	587	13.7	59.9		Yes	
141, 142	Secondary	Christenson	2001	62	15	19.5	63.1		Yes	Yes
143	Secondary	GAIN	2001	111	20	15.3	60.3		Yes	Yes
14–146	Mixed	EXCEL[a]	1991	1957	1348	40.8	55.8	Yes		
147;148	Mixed	Pravastatin Multi[a,f]	1993	815	247	23.3	55		Yes	
149	Mixed	Swiss Pravastatin	1993	37	13	26	51.5			
150	Mixed	CRISP	1994	91	195	68.2	71	Yes		
151, 152	Mixed	OCS	1994	351	64	15.4	63.6			
153–158	Mixed	WOSCOPS[a]	1995	6595	0	0	55.2		Yes	
159	Mixed	KAPS	1995	447	0	0	57.3		Yes	Yes
160	Mixed	CELL	1996	194	34	14.9	49.5			
161	Mixed	Eriksson	1998	516	495	49.0	53.3		Yes	
162	Not clear	Branchi	1995	15	15	50	53.9			
163	Not clear	Japanese Women	2000	0	56	100	51.3			
165, 166	Not clear	Muldoon	2000	104	90	46.4	46.4	Yes		
	All trials	All trials	–	41512	8733	–	–			

[a] Denotes a trial with at least 1000 patients.
[b] Year of publication is for main results paper.
[c] Patient numbers are for main comparison (i.e. two arms only) in trial only.
[d] Median age was used for Andrews and LIPID.
[e] Last three columns denote: any patients in USA, solely pharmaceutical company support, angiographic trial.
[f] 2 'gender-less' patients counted in with males in Pravastatin Multi.

TABLE 2 *Age- and sex-related characteristics of statins RCTs 1990–2001, according to location, source of funding and angiographic investigation*

	All RCTS	USA	Non-USA	Solely pharmaceutical	Not solely pharmaceutical	Angiographic	Non-angiographic
No. of RCTs	47	17	30	22	25	26	21
Median no. of patients (IQR)	270 (77–834)	270 (97–429)	267.5 (77–834)	427.5 (205–1062)	157 (56–305)	250 (97–408)	286 (56–4159)
No. of RCTs completely excluding women (%)	8 (17%)	1 (6%)	7 (23%)	6 (27%)	2 (8%)	6 (23%)	2 (10%)
Median no. of women across all trials (IQR)	45 (12–143)	80 (22–195)	22.5 (8–140)	53.5 (0–247)	34 (13–90)	22.5 (8–92)	64 (13–582)
Median % women across all trials (IQR)	18.6% (11.8–30%)	22.7% (15–40.8%)	16.5% (10.9–26%)	15.2% (0–19.5%)	29.9 % (14.9–46.9%)	15.8% (8.5–22.5%)	26% (15.1–49%)
No. of RCTs stating an upper age limit (%)	31 (66%)	12 (71%)	19 (63%)	18 (82%)	13 (52%)	19 (73%)	12 (57%)
Median upper age limit where reported (IQR)	70 (65–75)	75 (69.5–77)	70 (65–75)	70 (67–75)	70 (65–75)	70 (67–75)	70 (64.5–74)
No. of RCTs reporting proportion aged 65+ years (%)	13 (28%)	4 (24%)	9 (30%)	7 (32%)	6 (24%)	3 (12%)	10 (48%)
Median percentage aged 65+ years where reported (IQR)	0 (0–23%)	21.1% (10.3–60.7%)	0% (0–23%)	0 (0–23%)	10.3 (0–39%)	0 (0–0)	21.1 (0–33.1)

limit (75 vs 70 years, $p = 0.048$). USA trials also reported a higher median percentage of people aged 65+ years (21.1% vs 0%). The eight trials reporting ethnicity were all USA trials (median percentage of ethnic minorities 10.5%, IQR 7.5–15%). Because of this small number, we did not conduct any further analyses involving ethnicity. Only five trials included patients from the UK (FLARE, MAAS, Pravastatin Multinational Study, OCS, WOSCOPS); all of these except OCS and WOSCOPS also included patients from other European countries, so we did not perform any direct comparisons of UK trials with USA trials.

A total of 22 trials recorded a pharmaceutical company as sole source of external support. 'Solely pharmaceutical' trials were more likely to exclude women completely from their sample. Although, taken together, 'solely pharmaceutical' trials had a greater average number of women per trial, this was because they were relatively large studies compared with the other trials (median numbers 427.5 vs 157, $p = 0.004$), but in fact their median percentage of women was comparatively small (15.2% vs 29.9%, $p = 0.01$). The median value of the upper age limit in 'solely pharmaceutical' trials was similar to that for the rest of the series. A similar pattern emerged when we compared trials reporting **any** pharmaceutical support (not necessarily sole support) ($n = 38$) with trials reporting no pharmaceutical support at all ($n = 9$).

We classified 26 trials as 'angiographic'. These were more likely to exclude women and had smaller median numbers and percentages of women (15.8% vs 26%, $p = 0.018$). These trials were less likely to report the proportion of people aged 65+ years (12% vs 48%, $p = 0.009$).

All statins: conclusions

In RCTs of statins up to August 2001, women, older people and ethnic minorities were not well represented. USA trials tended to be more inclusive and angiographic trials less inclusive. Trials with commercial support had smaller proportions of women, but as part of larger samples.

Summary: all statins trials

- We analysed 47 RCTs of statins, with duration of at least 6 months.
- Six were for primary prevention, 29 for secondary prevention, with nine for 'mixed' primary/secondary and three which were not classifiable.
- USA trials were moderately more inclusive of women and older people than those conducted in other countries.
- Only eight trials, all from the USA, reported on inclusion of ethnic minorities.
- Angiographic trials tended to be less inclusive.
- Trials dependent on the support of pharmaceutical companies tended to have greater numbers of women, but as a smaller proportion of the sample.
- There was no clear relationship between commercial support and inclusion by age.

Statins secondary prevention: methods

In the following analyses, the trial series was restricted to a set of 'secondary prevention' trials, as defined above. However, we removed the two heart transplant studies from this set (Kobashigawa, Wenke), as the lipid profiles in such patients differ greatly from those of patients with the common forms of coronary artery disease. Thus, 27 trials were analysed as secondary prevention studies.

We extracted patients' characteristics (including cardiovascular co-medication) and corresponding numbers for those patients entered into the main analysis of the trial or, where this was not possible, for patients at the point of randomisation. Where low-density lipoprotein cholesterol (LDL-C) values were reported as mg/dl, we converted these data to mmol/l by multiplying by a factor of 0.02586 (as in LIPID and CARE). We calculated a mean net benefit for statins, in terms of reduction of LDL-C, by subtracting the average percentage reduction achieved in each control group from the average percentage reduction achieved in each experimental group. We then calculated the mean of these differences across the trials. For comparative purposes, we used trial event data to calculate crude mortality rates and also unadjusted relative risks of mortality with their standard errors. The weighted mean of these relative risks was calculated using the command 'metan' in STATA for Mantel–Haenszel fixed effects meta-analysis. We examined mortality and combined cardiovascular outcomes in detail for the four largest trials (as these contributed over 95% of the events in all the trials), including results for women, older people and ethnic minorities where these were reported.

TABLE 3 *Median minimum and maximum dosages of statins stipulated in secondary prevention trials of statins*

Type of statin	No. of trials	Median minimum dosage (mg)	Median maximum dosage (mg)
Atorvastatin	1	20	80
Fluvastatin	3	40	80
Lovastatin	8	20	80
Pravastatin	9	20	40
Simvastatin	6	15	40

We also present an overview of the design and results of two landmark studies published outside our time frame. The Heart Protection Study[184,185] was published in July 2002 and the PROSPER trial[186,187] in November 2002. We also noted ALLHAT-LLT,[188,189] published in December 2002, because of its ethnicity profile, which was markedly different from that of other statins trials.

Statins secondary prevention: results

Statins secondary prevention: results. Characteristics of trials

About half of the 27 secondary prevention trials had been published since 1997. Most trials involved a dietary regimen in both arms (19) and many varied the statins dosage to achieve a target lipid level (16). Dosages by type of statin are shown in *Table 3*. The control treatments were most frequently placebo, although in one trial the control was niacin (FATS) and in another placebo plus warfarin (ACAPS); four trials stipulated 'usual care' in the control arm, allowing treatment at the discretion of the patients' physicians. The mean follow-up period was 2.3 years. In all, 23 of the 27 trials reported at least some degree of commercial support.

Statins secondary prevention: results. Characteristics of patients

Number of patients

The total number of patients in these trials was 29,264 (median 331, IQR 131–834). Four trials each had >1000 participants, namely 4S, CARE, LIPID and GISSI-P, and together these accounted for 21,888 patients, that is, 75% of patients in this set.

Gender, age, ethnicity

Whereas no trials excluded men, five trials excluded women, giving a median proportion of women included of 16% (IQR 11–20%). In the 20 trials that stipulated an inclusion limit by maximum age, the median upper limit was 75 years (IQR 70–75). Mean ages per trial ranged from 48 to 67 years, the mean value of these means being 58.5 years. All trials excluding women had mean ages below the latter value, suggesting a relationship between average age of a trial and the proportion of women included. For the majority of trials it was difficult to discern how many participants were aged ≥ 65 years. Only four trials, all American (ACAPS, CARE, LCAS, PLAC-1), reported on the non-'white European' composition of their sample; the respective proportions were 7, 7, 12 and 18%. Non-'white Europeans' from these four trials contributed a total of 521 patients to this set of nearly 30,000 people although, in addition, three relatively small trials were conducted in Japanese or Taiwanese samples (Takagi, CARS, Su).

Cardiovascular co-medication

Cardiovascular co-medication was reported in a variety of ways and this present assessment should be regarded only as an approximate overview. We excluded non-statin lipid reducers given as 'rescue' medication during trials and drugs related solely to the period of revascularisation procedures, if these procedures had been performed as part of the trial protocol. In seven trials, the patients in both arms were encouraged to take aspirin as an integral part of their regimen. Apart from study medication, 17 trials reported usable data on cardiovascular co-medication, but this covered most patients (about 90%) from this set of trials.

Table 4 provides an overview of any data where trialists reported according to these major classes of drug. Co-medication in the four large trials is summarised in *Table 5*. These data suggest that in a typical trial the majority of patients were being prescribed aspirin (or were being encouraged to take it by the trialists). In fact, about half of patients were probably taking at least two cardiovascular medicines other than the experimental statin or the control 'drug' (probably

TABLE 4 *Percentage of patients (shown as medians and IQRs) on routine cardiovascular medication as reported in secondary prevention RCTs of statins*

Medication	No. of trials	Median (% patients)	IQR (% patients)
Beta-blockers	13	47	42–56
Diuretics	10	12	11–17
Calcium channel blockers	11	38	32–48
ACE inhibitor	11	11	8–20
Aspirin (non-study)[a]	11	79	56–84
Antiplatelet drugs[b]	3	14	11–56
Anticoagulants	2	17	2–32
Antiarrhythmics	2	3	2–4
Nitrates	11	45	33–56

ACE, angiotensin-converting enzyme.
[a] It was not always clear if aspirin usage predated the study.
[b] This class could have included non-study aspirin in some trials.

TABLE 5 *Percentage of patients on routine cardiovascular medication as reported in the four large secondary prevention RCTs of statins*

Medication	4S	CARE	LIPID	GISSI-P
Beta-blockers	57	40	47	43
Diuretics	7	11	17	11
Calcium channel blockers	31	39	35	32
ACE inhibitor	–	15	17	42
Aspirin (non-study)	37	83	82	79[a]
Other antiplatelet drugs	–	–	–	14
Anticoagulants	2	–	–	–
Antiarrhythmics	–	–	–	–
Nitrates	32	33	36	59

[a] Aspirin was not given as part of study but was recommended by the trialists.

most commonly an antiplatelet/aspirin plus antihypertensive and/or antianginal).

Exclusions for health reasons

Reasons for exclusions, which were commonly given, included child-bearing potential in women, life-threatening illness, cancer and different degrees of heart failure. A number of trials excluded patients with diabetes, usually if it required pharmaceutical treatment. Some excluded people with endocrine diseases and this, in theory, could also cover diabetes. However, patients with controlled diabetes were not excluded from the four large studies. Other common reasons for exclusion were gastrointestinal (GI) problems (in six trials), renal dysfunction (in 13 trials) and liver disease (in 18 trials).

Statins secondary prevention: results. Trial outcomes

Lipids

Baseline LDL-C values were reported as means in all but two trials (LIPID and Andrews), which reported these data as medians. The mean of these baseline LDL-C values in mmol/l was 4.10 [standard deviation (SD) 0.51] across both the statins and control arms. The average percentage reductions in LDL-C were reported as mean changes in 24 trials and as median changes in one trial. The mean of these change averages (not weighted by size of trial) was –30.1% (SD 7.2) across the statins arms and –4.5 (SD 8.1) across the control arms. We therefore estimated the mean net benefit achieved with statins in these trials (in terms of reduction of LDL-C) to be –25.9% mmol/l (SD 7.8).

Mortality

In all, 21 trials reported mortality data in a usable form. The weighted mean of the unadjusted relative risks for the 21 trials was 0.79 [95% confidence intervals (CI) 0.73 to 0.85], indicating that, on average, statins reduced the incidence of mortality by 21% relative to that in the control arm (see *Figure 3*). The four large trials accounted for about 95% of the weight in this pooling of risk

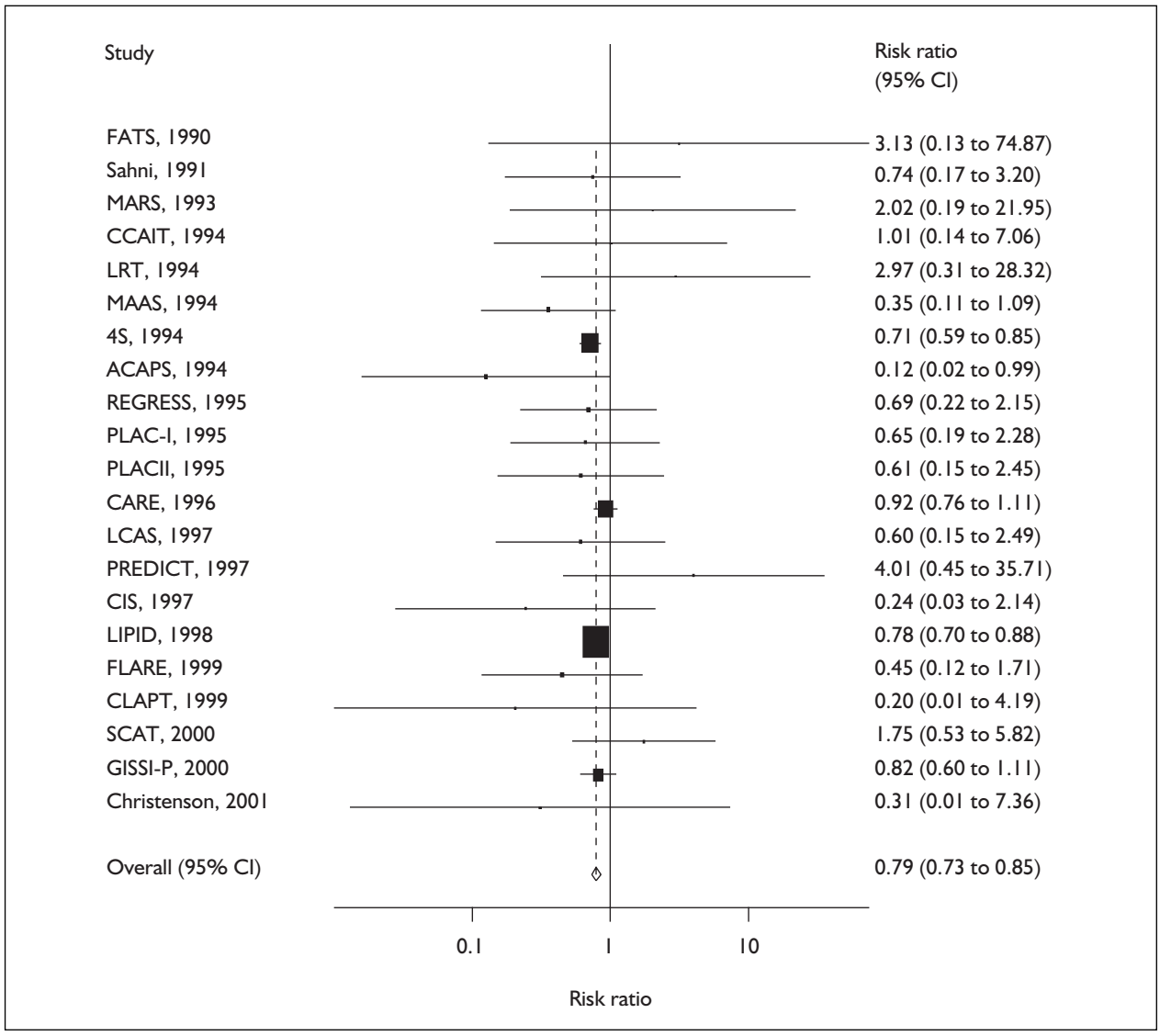


FIGURE 3 *Fixed effects meta-analysis of mortality events from statins trials of secondary prevention. The heterogeneity χ^2 statistic was 18.5, with 20 degrees of freedom,* p *= 0.56.*

ratios. *Table 6* summarises the mortality outcomes as reported in the four large trials. It should be noted that, broadly speaking, all the large trials, with the exception of 4S, included patients with total cholesterol levels that were in the normal range (i.e. ≤ 5.0 mmol/l), in addition to patients with elevated cholesterol levels. The mortality rates were relatively low in GISSI-P. The latter was an atypical trial in that the sample was Mediterranean, was filtered from a previous trial, some patients were taking fish oil, a group of higher risk control patients were switched to statins treatment during the study and the trial was closed early.

Combined cardiovascular end-points

The combination of cardiovascular outcomes used as the main cardiovascular end-point varied between trials. We selected the outcomes that were most comparable across the trials. These are summarised in *Table 7*. The results for 4S, CARE and LIPID all indicate sizable reductions in the risk of these events with statins treatment, in comparison with the respective control arms. The GISSI-P estimate is more modest and with a wider confidence interval, perhaps owing to a relatively low frequency of events in this trial.

Outcomes by gender

All of the four large trials reported on some of their major end-points according to sex. Mortality was not always reported according to sex. Their findings are summarised here but are considered in more detail later in the context of evidence-synthesis procedures (see Chapter 11). In GISSI-P the events and patients were too few to draw any

TABLE 6 *All-cause mortality outcomes from Cox regression analysis in the four large trials of statins*

Trial name[a]	Location	Mean follow-up period (years)	No. of patients	Total cholesterol values eligible for study (mmol)	Outcome estimate (95% CI)	Outcome estimator	Crude mortality rates (per 1000, statins arm vs control arm)
4S (1994)	Scandinavia	5	4444	5.5 to 8.0	0.70 (0.58 to 0.85)	Relative risk	82 vs 115
CARE (1996)	USA	5	4159	<6.2	9% (–12 to 26%)	Relative risk reduction	86 vs 94
LIPID (1998)	Australia/ New Zealand	6	9014	4.0 to 7.0	22% (13 to 31%)	Relative risk reduction	110 vs 141
GISSI-P (2000)	Italy	2	4271	Broad range	0.84 (0.61 to 1.14)	Relative risk	34 vs 41

[a] Pravastatin was the study drug in all these trials except 4S, which used simvastatin.

TABLE 7 *Combined cardiovascular outcomes from Cox regression analysis in the four large trials of statins*

Trial name	Mean age (years)	Outcome estimate (95% CI)	Outcome estimator	Outcome description	Crude event rates (per 1000, statins arm vs control arm)
4S (1994)	58.6	0.66 (0.59 to 0.75)	Relative risk	CHD death, non-fatal MI, resuscitated cardiac arrest	159 vs 226
CARE (1996)	59	24% (9 to 36%)	Relative risk reduction	CHD death or non-fatal MI	102 vs 132
LIPID (1998)	62	24% (15 to 32%)	Relative risk reduction	CHD death or non-fatal MI	123 vs 159
GISSI-P (2000)	59.9	0.90 (0.71 to 1.15)	Relative risk	Death, non-fatal MI or non-fatal stroke	56 vs 64

firm conclusions on differential effectiveness between men and women. In 4S no benefit in mortality was observed for women, although outcomes for men and women were similar for the combined cardiovascular end-point. In CARE, women appeared to benefit more than men in terms of the combined cardiovascular end-point. By contrast, in LIPID, women seemed to benefit less than men in terms of this end-point, but in both studies the relevant estimates were too imprecise to draw firm conclusions. The relevant data are reviewed as part of the evidence-synthesis procedures described in Chapter 11. We concluded that statins were at least as effective in women as in men for secondary prevention of death and combined cardiovascular outcomes.

Outcomes by age

All of the four large trials reported on the relative effects of statins for some of their major end-points according to age. Mortality was not always reported according to age group. The findings are summarised here but are considered in more detail in Chapter 11. The GISSI-P trial did not report any relative benefit in terms of the combined cardiovascular end-point for people aged ≥65 years, although lack of precision made it difficult to draw a firm conclusion. In 4S, patients aged ≥60 years received slightly less relative benefit than younger patients; there was a similar age differential for the combined cardiovascular outcome. In LIPID, the combined cardiovascular outcome was reported for a number of age bands;

the trend was for less relative benefit in older patients, with no clear benefit in patients aged ≥70 years. By contrast, in CARE, the relative benefit for the combined outcome was greater in patients aged ≥60 years than in younger patients. We reviewed the relevant data as part of the evidence-synthesis procedures described in Chapter 10. We concluded that statins were effective in older patients up to the age of 75 years for the secondary prevention of death and combined cardiovascular outcomes. Whether the relative risk reduction might be smaller than in younger patients is an interesting question but cannot be ascertained from the data available to us. An individual patient data meta-analysis might have sufficient power to assess the issue.

Outcomes by ethnicity

Although all four large trials presented at least some subgroup results pertaining to women and older people, none of the trials reported major outcomes according to ethnic group.

Severe adverse effects

Rhabdomyolysis

Only one case of rhabdomyolysis was reported in this set of trials, in a 60-year-old woman taking 20 mg of simvastatin daily in the 4S trial; symptoms resolved quickly after discontinuation and the investigators subsequently revised the diagnosis to myopathy as renal involvement was not observed. We then referred to the trials of primary and of mixed primary and secondary prevention. In the primary prevention AFCAPS/TEXCAPS trial with 6605 participants, one case of rhabdomyolysis in the lovastatin arm and two in the control arm were reported.

Breast cancer

Cases of breast cancer were only reported in 4S, CARE and LIPID. The numbers of cases (statins group versus control group) were 3 versus 6, 12 versus 1 and 10 versus 10, respectively. Of the 12 cases in the CARE pravastatin arm, three were re-occurrences and one occurred shortly after the start of the trial. In terms of all cancer incidence, there was no obvious excess in the statins arms in this set of trials. Referring to the trials of primary and of mixed primary and secondary prevention, we did not find any reports of cases of breast cancer. The assessment of severe adverse effects, such as breast cancer, of statins from the published trials is problematic as there is an inevitable tendency for data-dependent reporting of findings. The issue of potential hazards of cancers are discussed in more detail in Chapter 11.

Statins secondary prevention: large RCTs published after 1 August 2001

Heart Protection Study

The Heart Protection Study[184,185] was an RCT of 40 mg simvastatin daily compared with placebo, conducted in the UK. In a factorial design, patients were also randomised to a vitamin regimen or its matching placebo. To be eligible, patients had to be aged between 40 and 80 years and be at high risk of death due to CVD or to possess cardiovascular risk factors such as hypertension (in males ≥65 years old) or diabetes mellitus. Total cholesterol values were not required to be elevated for admission to the trial. A total of 20,536 people were entered into this trial, approximately the same number as in the four large secondary prevention trials combined. About 25% of the patients were women and 54% were aged >65 years, making this a relatively inclusive trial in these respects. A personal communication stated that 3.1% of patients were non-Caucasian. This compares with about 7% of the population in Great Britain, 2000–01.[190] Although strictly this was a 'mixed prevention' trial according to our typology, nearly all patients had manifestations of CVD.

The net reduction in LDL-C due to statins given as a study drug was 30% (one-fifth of control patients were prescribed a statin by their GP). In Cox regression analysis the relative risk of death from any cause in the statins-allocated group was 0.87 (95% CI 0.81 to 0.94), a risk reduction of 13%, whereas for CHD death or non-fatal MI the relative risk was 0.73 (95% CI 0.67 to 0.79), a risk reduction of 27%. Statins appeared slightly less protective in women than men and slightly less protective in older people (≥70 years old) than in younger people, but the differentials were small and were not statistically significant. This very large trial provided strong evidence that the effect of statins treatment was broadly similar among patients with a wide range of pre-existing CVDs, diabetes and cardiovascular risk factors. In terms of hazards, there were five cases of rhabdomyolysis in the statins arm and three cases in the control arm. With regard to breast cancer, there were 38 cases in the statins arms and 51 cases in the control arm. Hence outcomes in this large trial provide substantial evidence of benefit and do not support notions that statins cause rhabdomyolysis or breast cancer.

PROSPER

PROSPER,[186,187] conducted in Scotland, Ireland and The Netherlands, is worthy of note because it focused entirely on older men and women aged

70–82 years, randomly allocating them to 40 mg of pravastatin per day or placebo. Participants had a wide range of total cholesterol values but, in contrast to the Heart Protection Study, were evenly divided between people with and without evidence of diagnosed CVD. Of the 5804 participants, 51.7% were women. The relative risk of the combined cardiovascular outcome (CHD death or non-fatal MI or any stroke) was 0.85 (95% CI 0.74 to 0.97). This level of risk reduction was broadly in line with that observed for older people in previous trials. The reduction in the combined outcome for women [relative risk (RR) = 0.96, 95% CI 0.79 to 1.18] was not as favourable as that for men (RR = 0.77, 95% CI 0.65 to 0.92), but an interaction test did not suggest any difference between the results for men and women ($p = 0.13$). No benefit in terms of mortality rates was observed but the trial was not powered to achieve this. The trialists noted an overall excess of incident cancer in the pravastatin arm (245 cancers in the pravastatin arm versus 199 cancers in the placebo arm), but as such an excess had not been observed in the majority of previous large statins trials, the PROSPER trialists believed that this was probably a Type 1 error (a result specific to the PROSPER sample which was unlikely to be reproduced in other large samples).

ALLHAT-LLT

This study[188,189] formed the lipid-lowering component of the factorial Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT-LLT was conducted in the USA, Canada, Puerto Rico and the US Virgin Islands. The trial thereby accrued a proportion of ethnic group participants strikingly larger than any of the statins trials mentioned previously in this chapter, although this noteworthy achievement came very late in the experimental history of statins. The ethnic descriptions contained in the trial report are varied, but in total, 59% of the sample were non-white and non-Hispanic.

Participants were aged ≥55 years and had average to elevated levels of total cholesterol. About 14% had existing CHD, while the rest were considered at risk of CHD, making this a 'mixed prevention' trial, with a large majority of primary prevention patients. The comparison was of 20–40 mg of pravastatin versus usual care over 6 years. Limited benefits in terms of the combined cardiovascular outcome (CHD death or non-fatal MI) were observed (RR = 0.91, 95% CI 0.79 to 1.04). There was no evidence of benefit for all-cause mortality (RR = 0.99, 95% CI 0.89 to 1.11). These outcomes might be due to ALLHAT-LLT being an open trial in which about 30% of the control arm crossed over to statins use.

Statins secondary prevention: discussion

To our knowledge, this is the most comprehensive analysis of associations with inclusion of women, older people and ethnic minorities in a series of statins trials. It is worth emphasising that the Heart Protection Study, by virtue of its size, provides compelling evidence that the reductions in CVD outcomes of statins treatment for any specific subgroup are within the effect observed in the overall sample. In terms of hazards associated with treatment, a major problem is data-dependent reporting of adverse effects. This clearly applies to the breast cancer findings from earlier trials which are not apparent in the Heart Protection Study. The levels of inclusion in trials are compared with levels of need in the English population in Chapter 9, which deals with 'disparities'. Throughout the present chapter we have, to some degree, pre-empted these need levels by emphasising the relatively young and male nature of the trial samples throughout most of the experimental history of statins. Our approach was straightforward and transparent. We could be criticised for being over-simplistic in assuming that sex, age and ethnicity are the most important socio-demographic characteristics in this context. Furthermore, it could be argued that to possess adequate external validity, trial samples must adhere to a more subtle socio-demographic model than the model of 'need according to age, sex and ethnicity' that we had in mind. For example, no account has been taken of socio-economic position, which certainly increases need but is not routinely reported as a participant characteristic in trials. The issue of the diverse nature of individuals in need populations is discussed further in Chapter 13.

Statins secondary prevention: conclusions

In our set of RCTs of statins for secondary prevention, women and older people were not well represented. However, as a collective body of evidence, the trials provided sufficient information to show that women and older people up to the age of 75 years, benefited from statins. Ethnicity was poorly reported and major outcomes were not reported by ethnic group. Two later, large trials

paid more attention to the inclusion of women and older people and confirmed the effectiveness of statins for these groups. A third later trial addressed the ethnicity issue seriously, although mainly aiming at primary prevention. These three important studies came relatively late in the experimental history of statins.

Summary: statins secondary prevention trials

- We analysed 27 RCTs of statins for secondary prevention up to August 2001, containing 29,264 people.
- The four large trials in this set included people with total cholesterol levels in the normal range.
- The mean follow-up period was 2.3 years.
- The median proportion of women was modest, 16%, and five trials excluded women altogether.
- The mean of the average ages across the trials was 'pre-retirement', 58.5 years.
- Statins reduced the incidence of mortality, by a weighted average of 21%.
- The reduction in combined cardiovascular outcome in the three of the four large trials was of a similar or greater magnitude to this.
- The risk reduction in women provided by statins for the combined outcome was, on average, at least as great as that in men.
- Furthermore, older people, up to 75 years old, clearly benefited, although the extent of risk reduction may have diminished with age.
- Ethnicity was poorly reported and none of the trials reported outcomes according to ethnic group.
- Severe adverse events such as rhabdomyolysis appear to have been rare, with no excess observed in those taking statins.
- An excess of breast cancer was reported in only one trial in the set and was not confirmed in a much larger later trial.
- Two relevant landmark trials published after the close of our time frame reported results in broad accord with those in our set.

Chapter 4

Mapping trial participants and trial outcomes: NSAIDs

NSAIDs trials: background and objectives

NSAIDs are designed to produce, in regular dosage, both a lasting analgesic and an anti-inflammatory effect, appropriate in rheumatoid arthritis (RA) and in certain cases of advanced osteoarthritis (OA). Aspirin has been described as the 'prototype' Cox-1 NSAID, but it is now rarely prescribed for arthritis owing to its gastro-toxic properties and its effects on haemostasis. Trials of NSAIDs may have samples which are not representative of people who receive NSAIDs in the 'real world'. Accordingly, our main objectives were: to draw a sample of randomised NSAIDs trials; to ascertain the socio-demographic characteristics of the participants and investigate possible external influences on inclusion levels for women, older people and ethnic minorities and to describe outcomes in these trials, with a special focus on the rate of adverse events, identifying results specific to women, older people and ethnic groups.

NSAIDs trials: methods

We utilised an existing, comprehensive set of reports of trials of treatment for pain in OA. This had originally formed part of a large collection of articles used by Tallon and colleagues[191] in documenting the research priorities for this condition, as portrayed in the literature. The collection had been assembled after a search of the Cochrane Library, a search of MEDLINE and EMBASE up to March 1998 and a search of BIDS from 1981 to March 1998. Further details of the search are given in Appendix 3. However, we subjected the collection of trials to stricter criteria. To be eligible for our current investigation, studies had to be randomised trials for the treatment of OA with an NSAID in at least one arm. Trials in which two types or two dosages of NSAIDs were compared or in which an NSAID was compared with aspirin were acceptable. Trials with a cross-over design were included but we excluded '*N*-of-1' trials and trials in which the administration of the drug was not oral (non-oral administration featured in only six trials). Use of 'rescue analgesia', such as paracetamol, was deemed acceptable within a trial, and we did not impose any criterion pertaining to the length of the trial.

NSAIDs can be divided into two main classes, Cox-1 and Cox-2 NSAIDs, both of which are intended to reduce prostaglandin synthesis through inhibition of cyclooxygenase enzymes and, as a result, reduce inflammation. Cox-2s (also known as 'coxibs'), licensed in the UK since 1999, have been claimed to be more selective in their action than Cox-1 drugs and consequently less gastro-toxic and nephro-toxic. The possible adverse effects arising from Cox-2s and the degree to which some of the Cox-2 drugs have superior selectivity are the subject of continuing controversy, which would have made interpretation of the adverse events in our sample of trials more complicated. An overview of the issues surrounding Cox-2s is provided in Appendix 5. Moreover, our cohort of patients on NSAIDs, as described in Chapter 5, was established before Cox-2s were in common use. For these reasons, we decided to focus on trials of Cox-1 NSAIDs, for the purpose of our present study, and to regard aspirin as a separate class of drug from the other NSAIDs. We included trials with Cox-2s only if the trialists had compared the Cox-2 with a Cox-1, thereby adding to our understanding of Cox-1s. Trials that compared a Cox-2 with placebo were excluded.

After screening the collection of papers in this way, we stratified it, according to the number of patients covered in each paper ($n < 100$ in the first stratum, $n = 100$–199 in the second stratum, $n \geq 200$ in the third stratum) to gain a representative cross-section of RCTs of NSAIDs. Then, to produce a final sample of 25 RCTs, we randomly took an 11% sample of trials from each stratum. The process is depicted in *Figure 4*. For clarity, we drew upon only one treatment comparison per trial (e.g. Cox-1 arm versus placebo arm), taking the first comparison reported that met our criteria. In some instances this meant that the patient number used in our analysis was smaller than that for the paper as a whole, as we

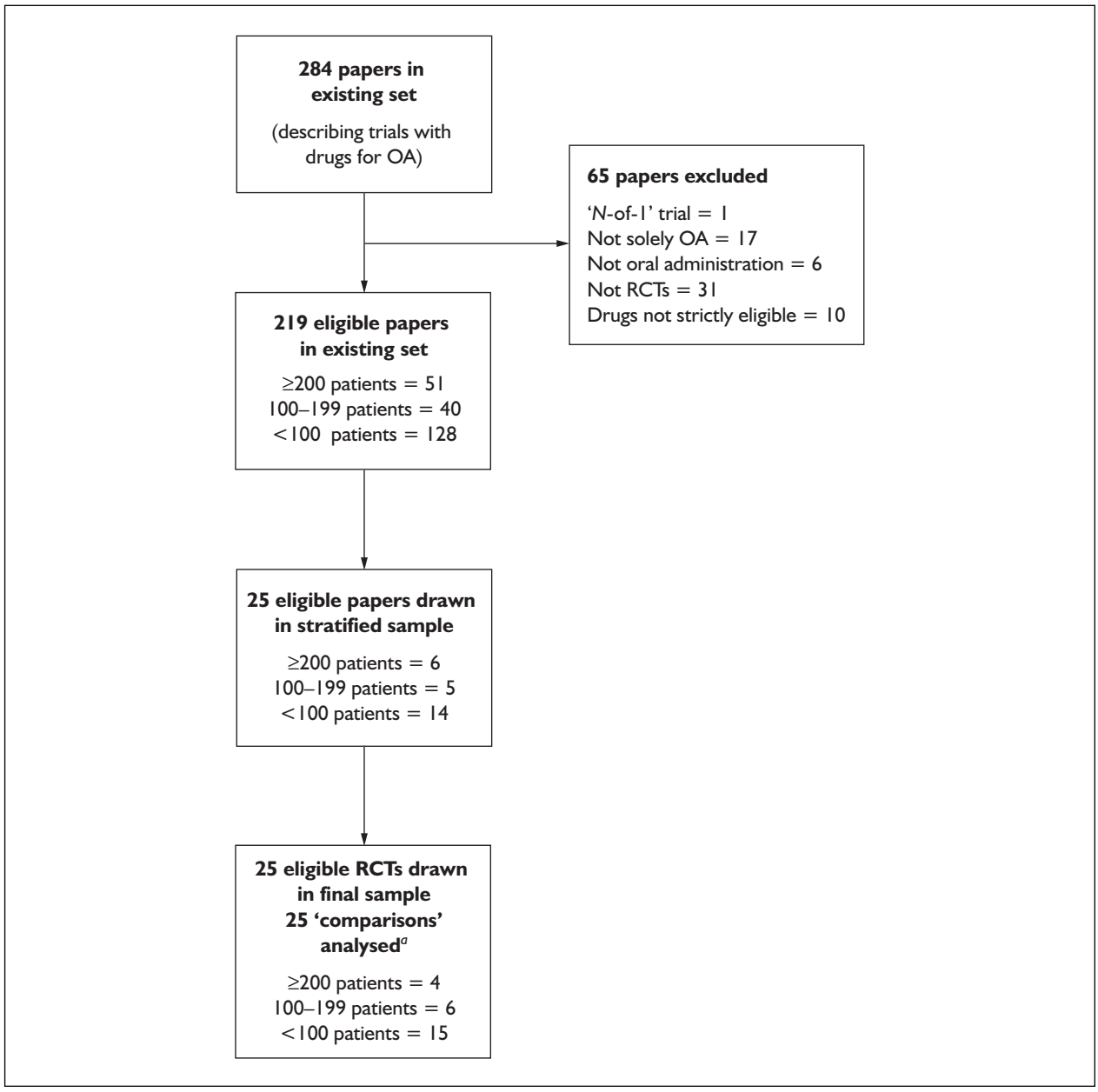


FIGURE 4 *Flowchart of stages of identifying eligible NSAIDs RCTs.* [a] *Only one comparison (e.g. NSAIDs arm versus placebo arm) was analysed per trial, although three trials contained more than two arms.*

ignored a third arm from that trial (this accounts for the different patient numbers indicated in the final two boxes of *Figure 4*). We extracted trial characteristics (such as types of drug, source of funding, location of research, inclusion and exclusion criteria) and patient characteristics (such as number, average age, percentage of women, ethnicity). If necessary, we approximated the mean age of all the patients in the comparison from any available data reported, such as mean ages for the NSAIDs arm and for the placebo arm.

Different NSAIDs were often compared with each other in the trials, resulting in various combinations of drugs under test. It would therefore have been uninformative for us to follow standard practice and concentrate on the outcomes from each trial as a whole (e.g. RR of an event on NSAID A as compared with NSAID B, RR of an event on NSAID C as compared with NSAID D, and so on). Instead, we focused on individual trial arms. We extracted serious adverse event data relating to the renal and GI systems and used these to calculate adverse event rates per 1000 patients, with standard errors (SEs), for each trial arm. Thus, we were able to produce a range of adverse event rates associated, in turn, with Cox-1s, Cox-2s, aspirin and lastly placebo. We also

TABLE 8 *Main characteristics of the 25 RCTs of NSAIDs in the sample (trials in order of year of publication)*

Ref.	Short trial name and year	No. of patients	Women (%)	Mean age (years)	Cross-over design	USA trial	Sole pharma-ceutical support	Cox-1 versus aspirin or placebo	Cox-1 versus Cox-1	Cox-2 versus Cox-1
192	Brooke, 1976	30	Not clear	Not clear	Yes	Yes	Yes	Aspirin		
193	Andrew, 1977	115	Not clear	Not clear		Yes	Yes		Yes	
194	Blechman, 1978	89	66	66.4	Yes	Yes	Yes	Placebo		
195	Andelman, 1980	65	83	66.5	Yes	Yes		Placebo		
196	Rubegni, 1981	44	57	Not clear			Yes	Aspirin		
197	Kogstad, 1981	149	64	67.6	Yes				Yes	
198	Verbruggen, 1982	21	76	Not clear	Yes		Yes		Yes	
199	Gengos, 1982[a]	234	68	Not clear			Yes		Yes	
200	Scharf, 1982	47	85	61.8	Yes				Yes	
201	Franchimont, 1982	22	86	64.5	Yes				Yes	
202	Boardman, 1983[a]	306	75	63	Yes			Placebo		
203	Williams, 1983	30	77	Not clear	Yes		Yes	Placebo		
204	Bobrove, 1983	97	77	62.5		Yes		Placebo		
205	Bird, 1985	30	53	61			Yes		Yes	
206	Mullen, 1987	37	68	58.5		Yes		Aspirin		
207	Goldberg, 1988	187	73	64		Yes	Yes		Yes	
208	Sarkar, 1988	60	62	50.2			Yes		Yes	
209	Chopra, 1989	121	51	61.4			Yes		Yes	
210	Brasseur, 1991	61	75	62			Yes			Yes
211	Pena, 1991	62	87	62.5			Yes			Yes
212	Alballa, 1992	67	66	52.4					Yes	
213	Eisenkolb, 1993	135	65	61			Yes			Yes
214	Torri, 1994[a]	205	62	57.3			Yes		Yes	
215	Perpignano, 1994	120	88	70.7			Yes			Yes
216	Schiff, 1996[a]	232	69	63.7		Yes		Placebo		
	All trials	2566	66	–	–	–			–	–

[a] Denotes a trial with at least 200 patients.

extracted one pain outcome and one movement outcome, which were the first (with usable data) reported for each comparison. The outcome data extracted were from the follow-up point closest to 4 weeks. In our results and summary, we refer to the comparison of interest as the 'trial'.

Data were extracted by one researcher, with extraction duplicated by a colleague for key variables. Analysis was in STATA 7, using Fisher's exact test and the Kruskal Wallis test.

NSAIDs trials: literature search results

NSAIDs trials: results. Characteristics of trials

Bibliographic references for all 284 papers in the existing collection are available from the authors. The 25 eligible RCTs drawn in the random sample[192–216] were all published during the period 1976–1996. The main characteristics of the 25 trials and their participants are summarised in *Tables 8* and *9*. Nine trials were of cross-over design, the remainder having a parallel arm design. Nine trials compared a Cox-1 (e.g. naproxen, ibuprofen) with placebo or aspirin, 12 compared a Cox-1 with a Cox-1 and four later trials compared a Cox-2 (etodolac) with a Cox-1. (Three of the Cox-1s, zomepirac, indoprofen and benoxaprofen, have had their licences withdrawn in the UK since the publication of the trial reports in our sample, reports which were all favourable.) Eight trials were carried out in the USA, five in the UK, nine in other European countries and four in developing countries. The majority, 16 of the 25 trials, reported receiving funding from the pharmaceutical industry but not from any other declared source.

Most trials (21) focused on patients with OA of the knee, and 11 of these also admitted patients with hip OA; two of the latter also admitted patients

TABLE 9 *Regimen characteristics of the 25 RCTs of NSAIDs in the sample. (Trials in order of year of publication)*

Short trial name	Experimental drug[b]	Dosage range of experimental drug (mg)	Withdrawn Cox-1? Cox-2?	Control drug[b]	Dosage range of control drug (mg)
Brooke	Fenoprofen	800–2400		Aspirin	1300–3900
Andrew	Diflunisal	500–750		Ibuprofen	800–1200
Blechman	Naproxen	750		Placebo	–
Andelman	Zomepirac	300	Withdrawn Cox-1	Placebo	–
Rubegni	Indoprofen	600	Withdrawn Cox-1	Aspirin	3000
Kogstad	Piroxicam	20		Naproxen	500
Verbruggen	Nabumetone	1000		Naproxen	500
Gengos[a]	Indomethacin SR	75		Indomethacin	75
Scharf	Naproxen	750		Diclofenac	150
Franchimont	Benoxaprofen	600	Withdrawn Cox-1	Indomethacin	75
Boardman[a]	Piroxicam	20		Placebo	–
Williams	Indomethacin SR	85		Placebo	–
Bobrove	Indomethacin	75–150		Placebo	–
Bird	Tenoxicam	40		Piroxicam	40
Mullen	Nabumetone	1000		Aspirin	3600
Goldberg	Naproxen SR	1000		Naproxen	1000
Sarkar	Ibuprofen SR	1200		Ibuprofen	1200
Chopra	Mefenamic acid	1500		Naproxen	1000
Brasseur	Etodolac	600	Cox-2	Diclofenac SR	100
Pena	Etodolac	600	Cox-2	Naproxen	500
Alballa	Nabumetone	1000		Diclofenac SR	100
Eisenkolb	Etodolac	600	Cox-2	Diclofenac	150
Torri[a]	Aceclofenac	200		Piroxicam	20
Perpignano	Etodolac SR	600	Cox-2	Tenoxicam	20
Schiff[a]	Naproxen SR	1000		Placebo	–

[a] Denotes a trial with at least 200 patients.
[b] SR denotes 'sustained-release' drug.

with spinal OA. Most trialists did not describe the trial's clinical setting (that is, primary care, secondary care, mixed), perhaps because most osteoarthritic pain will be treated in the community. No trials excluded by sex or by ethnic group. The median upper age across the trials for inclusion was 75 years (IQR 75–80) but an upper limit was only clearly reported in nine trials. Trials were, in general, brief. The follow-up point for outcome ranged from 2 to 26 weeks, with a median of 4 weeks. The follow-up point had been selected by us, of course, but for all except three trials this was also the final follow-up point stipulated by the trialists themselves. About three-quarters of the trials had durations of ≤6 weeks.

NSAIDs trials: results. Characteristics of patients

Numbers, gender, age, ethnicity

The NSAIDs trials tended to be relatively small. The total number of patients in the sample of trials was 2566, with a median of 67 patients (IQR 44–135). Women tended to be well represented, with 1693 in the sample. The median percentage of women across the trials was 69%, with a minimum of 52% and a maximum of 88%; two trials did not provide clear information on this point. In contrast, although prevalence of OA is age-related, about one-quarter of the trials had mean ages <60 years. We approximated (from the 19 trials with usable age data) the mean value of the mean ages across the trials as being 61.9 years (SD 4.88). Ethnicity was reported only in three USA trials and in one UK/European trial, with the median percentage of people from a non-'white European' background being 13% (range 2–17%). In addition, one trial was conducted in India (Sarkar) and one in Saudi Arabia (Alballa).

USA trials tended to be relatively large in comparison with non-USA trials (median patient numbers 93 vs 62) and contained, on average, a slightly greater proportion of women than non-USA trials (median percentages 71 vs 68). Likewise, trials with solely commercial support tended to have more patients than other trials

(median patient numbers 76 vs 67), but at the same time they tended to have a smaller proportion of women (median percentages 67 vs 75). Differences in approximated mean ages were only marginal but patients tended to be older in USA trials (median ages 63.9 vs 61.8 years) and younger in commercially supported trials (median ages 61.7 vs 63 years). None of these six sets of differences reached statistical significance at the conventional 5% level. The five UK trials tended to have a smaller percentage of women than non-UK trials (median percentages 65 vs 71) but the median age of UK participants was close to the non-UK median (61 vs 63 years).

Exclusions for co-morbidity or health reasons

Potential participants in these trials who had illnesses or physiological functioning which put them at risk of adverse effects from an NSAID were often excluded. Of the 25 trials, screening out at the selection stage was explicitly reported for GI problems by 15, for hepatic conditions by 11, for steroid use by 11 and for renal problems by 11. Actual thresholds for acceptable renal functioning were not usually reported. RA, haematological or haemostatic conditions, use of anticoagulants or possibility of pregnancy were also common criteria for exclusion. Eleven trials excluded patients who had experienced a previous adverse reaction to NSAIDs and/or excluded patients who had not benefited from previous NSAIDs use (e.g. Schiff, Gengos, Goldberg, Perpignano). Six trials reported the percentage of included patients who had used an NSAID before; the median was 100% (range 85–100%). In short, the participants in the trials in our sample were predominantly people who had used an NSAID before, who were at low risk of an adverse effect and who had an increased probability of achieving a beneficial outcome.

Description of co-medication

Existing medication in trial participants was not routinely reported. The possible interaction of NSAIDs with co-medication was not considered as a priority issue in the trial reports. This is an important deficiency since people with OA will be relatively old; they are likely to be taking one or more forms of vital medication, before NSAIDs treatment starts. Diuretics, for instance, are one example of a commonly prescribed medication which might have its action compromised by NSAIDs use.[217,218] Brooke was atypical in stating that all participants in the trial had existing illnesses, such as cardiovascular conditions and diabetes, although typical in not reporting any medication usage by patients, other than the use of study drugs.

NSAIDs trials: results. Trial outcomes

Severe adverse effects: renal events

These trials provided very little information on the effects of NSAIDs on renal functioning. Incidence of cases of renal failure (or of hospital admission with a renal diagnosis) was not explicitly reported in any of these studies, which gave the general impression that no renal dysfunction or renal compromise was likely to result from NSAIDs use. It is surprising that amongst these older people a few cases of renal compromise did not even occur, for reasons unconnected with NSAIDs, but on the other hand, as we have observed, the trials were mainly composed of people at low risk of an adverse event and the follow-up periods were short.

Severe adverse effects: ulcers and gastrointestinal bleeding

As *Table 10* shows, ulcers and GI bleeding were not well documented, with only six of the 37 Cox-1 arms reporting data for these significant conditions. The median rate amongst patients on Cox-1 of new or reactivated ulcer was 7.3 per 1000 (range 0–33.3), whereas for GI bleed (which in theory would have included the ulcer incidence) the median rate was 21.1 per 1000 (range 0–38.1). None of the Cox-2 or aspirin arms provided any data, except for one aspirin arm, which reported no ulcer problems. In a similar fashion, few relevant data were reported for placebo arms.

Severe adverse effects: gastrointestinal drop-outs

The category of drop-outs for GI conditions was relatively well documented for the drugs in these trials (*Table 10*). Evidently, most trialists regarded this broad category as the most important end-point, or at least as the most convenient one to record. The median drop-out rate in Cox-1 arms was 39.2 per 1000 patients with a range from 0 to 333.3. *Figure 5* presents GI drop-out rates for Cox-1 arms from trials with at least 200 patients. The respective 95% CIs are also shown to demonstrate the relatively low statistical precision of most of these estimates. For example, the rate reported by Schiff was 60.3 per 1000 (95% CI 17.0 to 103.7). Furthermore, it was difficult to interpret these rates, as they could encompass comparatively mild problems, such as indigestion or heartburn, in addition to serious and well-defined conditions such as stomach ulceration and GI bleeding.

The broad drop-out category was also well reported for Cox-2, aspirin and placebo arms, patients on the active drugs tending to have higher GI drop-out rates than Cox-1 patients. Overall, though, the picture of adverse events

TABLE 10 *Selected adverse events by drug type from individual trial arms. (Rates are patients with event of interest per 1000 patients)*[a]

	New or reactivated ulcer	GI bleed	Drop-out for any GI reason
Median rate per 1,000 (range) on Cox-1	7.3 (0–33.3)	21.1 (0–38.1)	39.2 (0–333.3)
Proportion of relevant trial arms reporting this (patient denominator)	6 of 37 (666)	6 of 37 (657)	25 of 37 (2861)
Median rate per 1000 (range) on Cox-2	No values	No values	62.1 (62.5–75.8)
Proportion of relevant trial arms reporting this (patient denominator)	0 of 4 (0)	0 of 4 (0)	3 of 4 (158)
Median rate per 1000 (range) on aspirin	0	No values	62.1 (33.3–90.9)
Proportion of relevant trial arms reporting this (patient denominator)	1 of 3 (30)	0 of 3 (0)	2 of 3 (52)
Median rate per 1000 (range) on placebo	0	16.9 (0–33.7)	10.5 (0–11.2)
Proportion of relevant trial arms reporting this (patient denominator)	1 of 6 (72)	2 of 6 (395)	4 of 6 (582)

[a] By definition, in any given trial, ulcer cases might possibly also contribute to GI bleed figures, and ulcer cases and GI bleed cases might also contribute to the GI drop-outs.

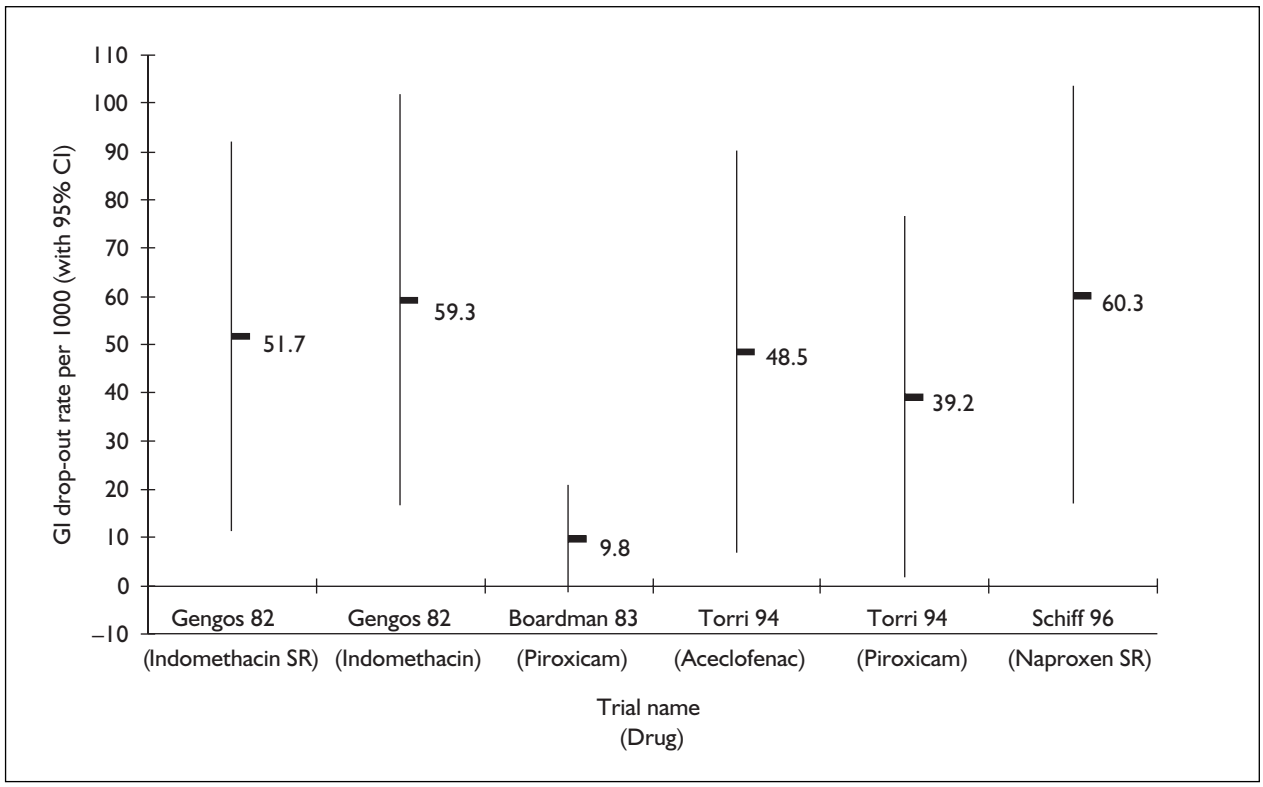


FIGURE 5 *GI drop-out rates per 1000 patients on Cox-1 NSAIDs by trial arm in trials with ≥200 people (with 95% CIs)*

associated with NSAIDs in these trials was clinically incomplete and statistically imprecise.

Pain and movement outcomes

The pain and movement measurements used as efficacy outcomes varied between trials. In fact, batteries of different measures were often used within trials. It was common to use a visual analogue scale (VAS) to quantify pain, which could be completed by the patient and/or the physician, and to summarise these measurements using a mean value. Sometimes four- or five-point Likert-type scales were used, which tended to be of unknown provenance and to be unsupported by a statement of their clinimetric properties. The aspects of pain measured were most frequently day pain, night pain, pain on active movement and pain on passive movement and pain on weight-bearing. The movement measure most frequently used was knee flexion in degrees, although walking time over a set distance and hip abduction also featured. Measures of patient preference were also sometimes used.

The problem of the multifarious outcome measurements used in rheumatology has been highlighted by Bellamy.[219,220] There is no general agreement on which are the most useful domains to measure or the most valid instruments to use. For these reasons we have not attempted a quantitative summary or synthesis of the efficacy outcomes in these trials. This might form a challenging task for an enthusiastic systematic reviewer in the future. All trials, however, reported definite benefits from NSAIDs treatment (from both Cox-1s and Cox-2s) in terms of decreased pain and increased movement. However, it is debatable what these trials, as a body, contribute to our understanding of the benefits of NSAIDs, owing to the relatively small number of patients involved, the different types of outcomes reported and the problematic nature of many of the measurements.

Outcomes and adverse effects by gender

Adverse events, pain and movement outcomes were not reported separately by sex in any of these trials. As we have noted, the majority of participants were women, so if there are sex-related differences in the effects of NSAIDs, the sample of trials is slightly more relevant to women than to men.

Outcomes and adverse effects by age

Pain and movement outcomes and adverse events were generally not reported for comparative age groups. There were two exceptions. In Boardman, it was observed that older people (≥70 years) in hospital did not always achieve the same beneficial pain and movement outcomes as the younger people in the sample. In Sarkar it was observed that overall adverse events occurred about three times more frequently in people aged >50 years compared with younger people.

Outcomes and adverse effects by ethnicity

Pain and movement outcomes and adverse effects were not reported separately for ethnic groups in any of these trials.

NSAIDs trials: discussion

Our sample of trials was not large, but it was drawn from a broad sampling frame and it furnished a definite pattern of inclusion levels in NSAIDs trials. A comparison of harms and benefits resulting from NSAIDs treatment would have strengthened our analysis, but as we have stated, the different measurements used for pain and movement outcomes of NSAIDs present a considerable problem in themselves. As with statins, our approach was straightforward and transparent, but could be criticised for being over-simplistic in not taking account of the diverse nature of potential recipients of treatment (see Chapter 13).

NSAIDs trials: conclusions

Most NSAIDs trials in our sample were commercially supported and this probably affected inclusion levels. On the other hand, USA trials tended to be more inclusive. Overall, the average age was only slightly more than 60 years but, in contrast with statins trials, women were well represented. Ethnicity was poorly reported. Outcomes were seldom reported by socio-demographic group. Clinical inclusion criteria seem to have screened out many participants at risk of GI events and virtually all at risk of renal compromise. NSAIDs trials for pain in OA are not well designed for the people most in need of treatment, that is, older people who will commonly have co-morbidities, co-medication and less efficient physiological functioning. Reports of NSAIDs trials may underestimate the level and type of adverse events likely to occur in 'real world' populations of patients.

Summary: NSAIDs trials

- We utilised a comprehensive set of about 300 trials for osteoarthritic pain, extending to the late 1990s.

- We analysed a stratified sample of 25 RCTs of NSAIDs (predominantly Cox-1s) for OA.
- The majority of trials had received funding from the pharmaceutical industry.
- The trials were brief and relatively small, most lasting ≤6 weeks, with a median of 67 patients.
- Women were well-represented, the median percentage across the trials being 69%.
- The mean of the average ages across the trials was 61.9 years.
- USA trials tended to be more inclusive of women and older people, but commercially supported trials were less inclusive.
- Ethnicity was not well reported, but was better documented in USA trials.
- Participants were mainly people known to benefit from NSAIDs or who were not liable to suffer adverse events.
- Drop-outs due to GI complaints were reported in about two-thirds of trials (median rate 39.2 per 1000 patients in Cox-1s).
- More serious GI adverse events were poorly reported.
- Outcomes, including adverse events, were seldom reported according to sex, age or ethnic group.
- NSAIDs trials may underestimate the extent of adverse events, in particular renal events, that would be experienced by 'real world' populations using these drugs.

Chapter 5

Patient cohorts: statins

Statins cohort: background and objectives

Patients who are prescribed statins in routine clinical practice may differ from those people who receive statins in clinical trials and may have different outcomes from the latter. Accordingly, our main objectives were: to identify a cohort of people who might benefit from secondary prevention with statins; to characterise these people socio-demographically and clinically, to identify people who were or who were not prescribed statins; to follow up the cohort to determine the association between treatment with statins and cardiovascular and mortality outcomes; and to examine the extent to which other cardiovascular medications were used in conjunction with statins.

Statins cohort: methods

Record linkage

The Tayside Medicines Monitoring Unit (MEMO) (Dundee) provided a robust method of identifying and following up a cohort of patients within Tayside who could potentially have benefited from statins after a hospital episode involving CHD.

MEMO was set up to detect and quantify serious drug toxicity in the community, using record linkage techniques.[221] MEMO currently utilises data from the Tayside Health Board area of Scotland, which serves over 400,000 patients and has about 63,000 NHS hospital discharges per annum. The rate of patient migration out of the area is low. The system is built around prescriptions given by family doctors throughout Tayside and subsequently dispensed through community pharmacies. The patient's name and address on the scripts are used by MEMO workers to achieve linkage to a unique Scottish NHS patient number (Community Health Index number or CHI number), which is then used to link to other NHS datasets such as hospital discharges, outpatient attendances, endoscopies and pathology laboratory reports, and to socio-demographic descriptors. Mortality data are obtained from hospital records and Registrar General certifications. Hospital episode data in MEMO extend back to 1980. Drug exposure data for selected medicines were collected from 1989, and all medicines were included from 1993 onwards.

Study population and cohort

The study population was composed of all residents of Tayside registered with a family doctor for the years 1993–1996 (the 'study window'), or from 1 January 1993 until their date of death if they died before the end of the study window. Patients who migrated from Tayside during the study window were not included. The study cohort was composed of those people in the study population who were discharged from Tayside hospitals during the study window with a diagnosis of MI or after receiving a coronary artery bypass graft (CABG).

Exposures

Exposures included the sex of patients and age at discharge and the dispensing of any of the following cardiovascular drugs during the follow-up period: beta-blockers, ACE inhibitors (ACEIs), anti-platelet drugs (including aspirin) and warfarin. We also included as an exposure group other drugs (i.e. excluding ACEIs and beta-blockers), which could be used as antihypertensives. Carstairs deprivation scores, derived from patients' postcodes and 1991 Census data, were divided into six categories with 'Category 1' being the most affluent category.[222,223] No analyses by ethnic group were possible, however, because sufficient ethnicity data were not routinely collected within the NHS in Tayside at this time.

The main division in the cohort, however, was between those who were 'statins users' after their hospital episode (patients who had a statin prescribed and dispensed for them) and those who were 'non-statins users' (for whom statins had evidently not been considered appropriate by a physician). Treatment with statins could begin at point of discharge or be initiated later by a family doctor. For each statins user we estimated adherence to the statins regimen in an approximate fashion: we totalled the number of days covered by statins prescriptions during follow-up and regarded these days as a continuous

TABLE 11 *Characteristics of post-MI and CABG-patients according to statins treatment, 1993–96*

		Statins treatment (n = 729)	Non-statins treatment (n = 2459)	p-Value
Disease type	MI	489 (67.1%)	2100 (85.4%)	
	CABG	240 (33.0%)	359 (14.6%)	<0.0001
Age (years)[a]	<45	53 (7.3%)	63 (2.6%)	
	45–54	161 (22.1%)	243 (9.9%)	
	55–64	252 (34.6%)	578 (23.5%)	
	65–74	217 (29.8%)	785 (31.9%)	<0.0001
	75+	46 (6.3%)	790 (32.1%)	
Sex	Male	461 (63.2%)	1502 (61.1%)	
	Female	268 (36.8%)	957 (38.9%)	0.293
Beta-blocker use	Yes	381 (52.3%)	865 (35.2%)	
	No	348 (47.7%)	1594 (64.8%)	<0.0001
ACEI use	Yes	283 (38.8%)	772 (31.4%)	
	No	446 (61.2%)	1687 (68.6%)	0.0002
Antihypertensive use (not ACEIs or beta-blockers)	Yes	19 (2.6%)	80 (3.3%)	
	No	710 (97.4%)	2379 (96.8%)	0.376
Anti-platelet use	Yes	572 (78.5%)	1668 (67.8%)	<0.0001
	No	157 (21.5%)	791 (32.2%)	
Warfarin use	Yes	90 (12.4%)	225 (9.2%)	
	No	639 (87.7%)	2234 (90.9%)	0.011

[a] Trend test, $p < 0.0001$.

period for which the medication was intended; if any prescription was redeemed by the patient too late after the previous prescription to maintain continuous use, we regarded the gap as a period of non-adherence, quantifiable as a percentage of time of intended use. Adherence was approximated for descriptive purposes only and we did not make any statistical adjustments in our outcome analyses to take account of different degrees of adherence.

Outcomes

The two outcomes of interest in the follow-up were a combined cardiovascular outcome (cardiovascular mortality or a new non-fatal MI) and death from any cause (all-cause mortality).

Statistical models

We used the χ^2 test to determine statistically significant differences between the characteristics of statins users and non-statins users, performing the Cochran–Armitage trend test if there were more than two categorical variables. In the analysis of the outcomes we calculated adjusted hazard ratios with 95% CIs in Cox regression models with a time-dependent variable for statins use. The other covariates in the models were age, sex, Carstairs category and the different types of cardiovascular co-medication mentioned above. Data were analysed in SAS 8.

Statins cohort: results

Statins cohort: results. Characteristics of patients

A total of 3188 patients were included in the study cohort. All these people could potentially have benefited from statins treatment for secondary prevention. However, only 729 (23.4%, 95% CI 21.9 to 24.9%) were prescribed statins after discharge from hospital. In all, 77% of these statins users had adherence at a level greater than 80%. *Table 11* compares the characteristics of statins users and non-statins users. In comparison with non-statins users, statins users were more likely to have undergone a CABG and were less likely to have a diagnosis on discharge of MI. The younger age groups were well represented amongst statins users, almost one in three of the latter being aged <55 years, while the corresponding figure for the non-statins users was

TABLE 12 *Distribution of selected combinations of cardiovascular drug use amongst men and women in the study cohort, 1993–96*

Drug use	Men	Women	*p*-Value
No statin	1502 (82.5%)	957 (84.4%)	0.13
Statin alone	17 (0.9%)	18 (1.6%)	
Statin + antiplatelet (A)	79 (4.3%)	42 (3.7%)	
Statin + beta-blocker (B)	41 (2.3%)	13 (1.2%)	
Statin + ACEI (C)	19 (1.0%)	7 (0.6%)	
Statin + A, B	116 (6.4%)	67 (5.9%)	
Statin + A, B, C	47 (2.6%)	30 (2.7%)	
Statin + any other antihypertensive	0	0	

TABLE 13 *Outcomes for post-MI and -CABG patients according to statins treatment, 1993–96*

		Statins treatment (*n* = 729)	Non-statins treatment (*n* =2459)	*p*-Value
Cardiovascular death or recurrence of MI	Yes	42 (5.8%)	581 (23.6%)	
	No	687 (94.2%)	1878 (76.4%)	<0.0001
Death from any cause	Yes	21 (2.9%)	440 (17.9%)	
	No	708 (97.1%)	2019 (82.1%)	<0.0001

TABLE 14 *Univariate and multivariate relative risks (hazard ratios, with 95% CIs) for combined cardiovascular outcome and mortality in statins users compared with non-statins users, 1993–96*

	Univariate	Multivariate[a]
Cardiovascular death or recurrence of MI	0.37 (0.26 to 0.55)	0.59 (0.40 to 0.87)
All-cause mortality	0.32 (0.19 to 0.51)	0.58 (0.36 to 0.96)

[a] Multivariate analyses were adjusted for age, gender, social deprivation and use of those cardiovascular drugs listed in *Table 11*.

about one in eight. At the higher end of the age range there was also disparity, only 6.3% of statins users being ≥75 years of age compared with 32.1% of non-statins users. Men predominated amongst both users and non-users, but women constituted similar proportions amongst users and non-users, 36.8 and 38.9%, respectively.

Statins users were more likely to take beta-blockers, ACEIs, antiplatelet drugs and warfarin, but for most drugs the difference in proportions between the statins users and non-users was only moderate, although statistically significant. Beta-blockers were a notable exception, with a greater differential between statins users and non-users, the respective proportions being 52.3 and 35.2%. In fact, virtually all statins users were also taking another form of cardiovascular medication (*Table 12*). It is possible that physicians who prescribed statins had a tendency to be more active prescribers of cardiovascular medication in general. *Table 12* shows selected combinations of cardiovascular medication in men and women. The most common scenario, amongst both male and female users of statins, was for a statin to be prescribed in combination with beta-blockers and antiplatelet drugs (statin + A, B).

Statins cohort: results. Cardiovascular and mortality outcomes

Hazard ratios (adjusted for all factors in the analyses) are plotted in *Figures 6* and 7. The pattern of independent RRs was similar for both outcomes of interest, as the figures show. For example, the RR of both all-cause mortality and CVD outcomes increased steadily by age group, as one would expect, death being about six times more probable in someone aged ≥75 years than in someone aged ≤44 years. The RR of mortality was also greater in men than women. Use of statins,

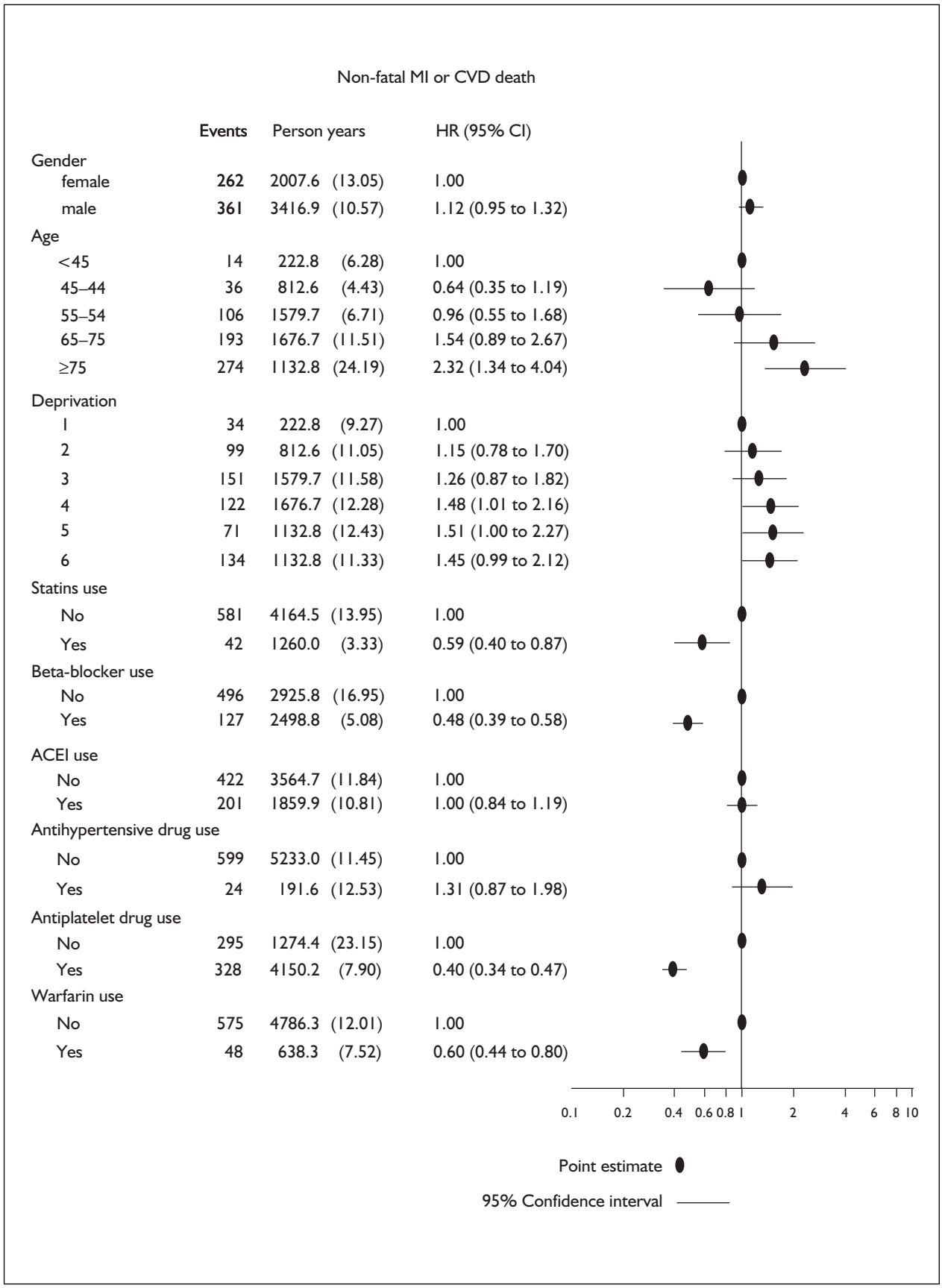


FIGURE 6 *Adjusted hazard ratios for combined cardiovascular outcome in post-MI and -CABG patients, 1993–96 (adjusted for all factors included in the figure). Log scale used. Hazard ratio <1.00 indicates a diminished risk relative to reference category. Antihypertensive drug use excludes beta-blockers and ACEI.*

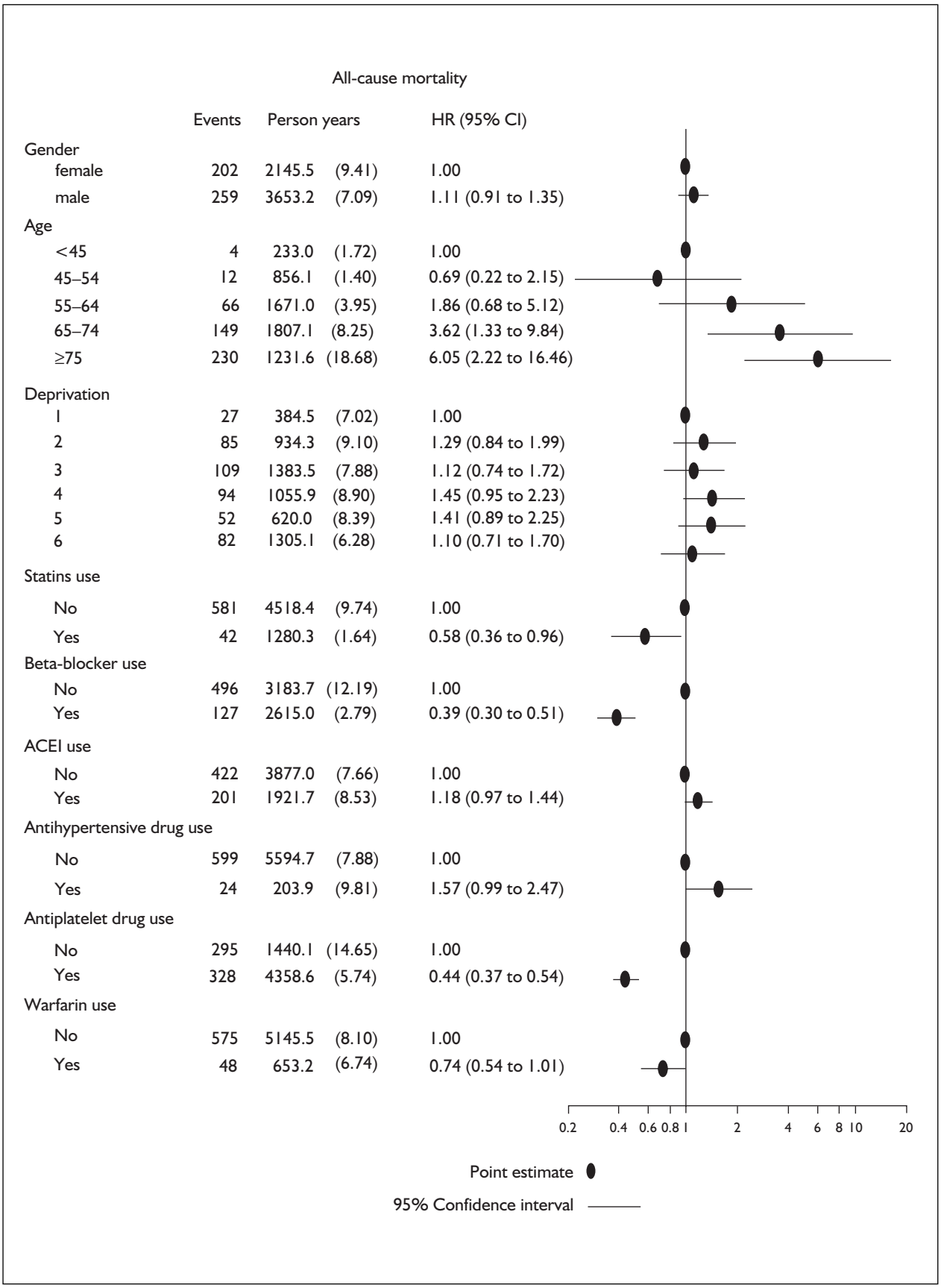


FIGURE 7 *Adjusted hazard ratios for all-cause mortality outcome in post-MI and -CABG patients, 1993–96 (adjusted for all factors included in the figure). Log scale used. Hazard ratio <1.00 indicates a diminished risk relative to reference category. Antihypertensive drug use excludes beta-blockers and ACEI.*

use of beta-blockers, use of antiplatelet drugs and use of warfarin were each independently associated with diminished risk. Conversely, use of ACEIs and use of other antihypertensives (other than beta-blockers and ACEIs) were both independently associated with increased risk, although these risks did not reach statistical significance at the 5% level. However, use of ACEIs was not associated with the combined cardiovascular outcome (*Figure 6*). Although we had ascertained the number of patients receiving various combinations of cardiovascular drugs, the event numbers for these combinations were too small for an investigation of possible synergistic effects which they might produce (*Table 12*).

As *Tables 13* and *14* show, statins appear to be a highly effective mode of secondary prevention in this 'real world' cohort. In statins users, the RR of a recurrence of the combined cardiovascular outcome was reduced by >60%, the hazard ratio being 0.37 (95% CI 0.26 to 0.55). The reduction in the RR for all-cause mortality was slightly greater. As we have noted, statins users had a different risk profile to non-statins users, thereby exaggerating these non-randomised estimates of treatment effect. The risk reduction for the combined cardiovascular outcome was about 40%, the adjusted hazard ratio being 0.59 (95% CI 0.40 to 0.87), and the adjusted risk reduction for mortality from any cause was of the same magnitude. The extent to which adjusted estimates can provide control for measured confounders is limited and these estimates of the statins treatment effects are likely to be seriously affected by unmeasured, and unknown, confounders which would not influence randomised trial estimates.

Statins cohort: discussion

Statins users differed markedly from non-users in terms of age distribution, past medical history and use of drug treatments for secondary prevention. The majority of statins users were also being treated with other cardiovascular drugs. In the non-randomised comparisons presented here, statins users had a greatly diminished risk of unfavourable outcomes in comparison with non-statins users. This was no doubt due to the relative youth of the statins users, their less adverse risk profile and their more frequent treatment with a range of cardiovascular medicines, which probably provided independent therapeutic benefit. After statistical adjustment, statins were still associated with an apparently large beneficial effect – a risk reduction of about 40% for both the combined cardiovascular outcome and for all-cause mortality. However, this effect is likely an overestimate explained by selection of patients with a more favourable prognosis for treatment and confounding effects which are avoided in randomised trials.

Ideally, adjustment for all other factors of possible influence such as other co-morbidities (in particular diabetes), smoking, other health-related behaviours and the severity of CHD would be desirable. In a methodological review, Britton and colleagues[224] found in their set of case studies that baseline prognostic factors in non-randomised studies influenced study results only slightly, but the direction of influence was not consistent. Some more dramatic examples arising from confounding in cohort studies have been discussed by Davey Smith and Ebrahim.[225]

For most of the period in question (1993–96), the evidence base for statins remained limited. With respect to secondary prevention, the main results from 4S[89] were published in 1994, whereas those from CARE[117] were published in 1996. Both of these studies had samples with mean ages of <60 years and proportions of women <20%. Two 'mixed prevention' trials were also published during this period. Again, both of these trials had mean ages of <60 years, but EXCEL (publishing its main results in 1991[145]) contained a large proportion of women, 41%, although WOSCOPS (publishing its main results in 1995[153]) contained only men. We might speculate that physicians in Tayside preferred to prescribe statins for younger patients (rather than to risk them in older people with more complicated problems), but considered it appropriate to prescribe statins for women.

Comparatively little longitudinal observational research has been done on outcomes with statins. Researchers using an earlier version of the MEMO database, covering the wider period 1985–95, followed up 5590 patients with an incident first MI, thus overlapping slightly with the present study. In this earlier investigation, outcomes on statins, adjusted for socio-demographic and co-medication variables, were also similarly favourable. Patients with good adherence to statins had an adjusted hazard ratio of 0.47 (95% CI 0.22 to 0.99) for all-cause mortality in comparison with people who had no statins treatment or had moderate or poor adherence to statins.[226]

We had anticipated that the outcomes observed in a non-randomised study would be less, rather than

more, favourable than those produced in randomised trials in which optimum care can be delivered. Typically, health gain is lost as successive steps from the trial findings to considerations of population coverage, diagnostic accuracy, physician compliance with treatment protocols and patient adherence to treatments are traversed in assessing treatment in the community.[227]

Statins cohort: conclusions

We identified a 'real world' cohort of people in Tayside who might benefit from secondary prevention with statins. Physicians treated only a minority of patients who might benefit with statins. Statins users tended to be younger than non-statins users, and tended to be prescribed cardiovascular co-medication. Sex was not a factor 'per se' in the differential prescribing. It is likely that the statins users in the cohort were a 'good prognosis' group. Cohort data must be analysed and interpreted carefully. If account is not taken of the socio-demographic profile and the clinical characteristics of patients, projections of the general level of effectiveness of a treatment may be very misleading. Databases such as MEMO require maintenance and long-term funding if they are to be useful. A particular strength of large observational cohorts is their ability to uncover potentially hazardous or unexpected drug effects. For example, analyses of the General Practice Research Database have described an association between statins use and lower risk of dementia.[228] However, such databases need to be large to capture rare drug effects.

Summary: statins cohort

- We used record linkage to follow up a cohort of 3188 individuals who needed secondary prevention for CHD after discharge from hospital.
- The setting was Tayside, Scotland, during the period 1993–96.
- Only 23% of the cohort were treated with statins during follow-up.
- Physicians prescribed statins preferentially, apparently being cautious with regard to age but not with regard to sex.
- Statins users tended to be younger than non-statins users and were more frequently prescribed cardiovascular co-medication.
- Men predominated amongst both statins users and non-statins users.
- Statins users had better cardiovascular and mortality outcomes than non-statins users.
- Most types of cardiovascular co-medication also provided independent therapeutic benefits.
- Statins reduced by about 40% the risk of recurrent MI and cardiovascular death, and of all-cause mortality (after statistical adjustment for socio-demographic variables and co-medication).
- Statins were given to a minority in this cohort and we were not able to adjust for all important variables, such as co-morbidities, and age–drug interactions in the analyses.
- This high level of effectiveness may not be generalisable to all population groups.
- Cohort data may greatly over- or underestimate the general effectiveness of drugs, despite taking careful account of the profile of patients and other variables.

Chapter 6

Patient cohorts: NSAIDs

NSAIDs cohort: background and objectives

The BNF[190] urges caution in the prescribing of Cox-1 NSAIDs to a wide range of potential users, such as people with a history of gastric problems, people with cardiovascular syndromes and elderly people. It strongly urges monitoring of patients with pre-existing renal problems who take NSAIDs and states that NSAIDs treatment is contraindicated for people with peptic ulceration.

With the possibility of such adverse outcomes in mind, we wished to ascertain how far people who are prescribed NSAIDs in the 'real world' differ from people who receive NSAIDs in clinical trials and whether the former have different outcomes from the latter. Accordingly, our main objectives were: to follow up a 'real world' community cohort of NSAIDs users; to characterise these users socio-demographically and also according to factors that are contraindications for NSAIDs prescription or indications for caution; and to determine the association between exposure to these factors and the rates of adverse event outcomes.

NSAIDs cohort: methods

Record linkage

The history and design of MEMO are described at the beginning of Chapter 5. MEMO provided an efficient means of identifying and following up a cohort of patients who were using Cox-1 NSAIDs and of quantifying their exposure to this class of drugs.

Study population and cohort

The study population was composed of all residents of Tayside registered with a family doctor during the years 1989–96 (the 'study window'), or from 1 January 1989 until their date of death if they died before the end of the study window. Patients who migrated from Tayside during the study window were not included in the study population. The study cohort consisted of patients in the study population who were dispensed NSAIDs in any form for any medical condition during the study window. We assumed that the NSAIDs prescribed during the years in question would, with few exceptions, be Cox-1 NSAIDs.

It was conceivable that a patient might have several brief exposures to NSAIDs at widely separated points during the 7 years of the study window. As we wished to focus on more continuous, concentrated exposures, we adopted the following procedures. We defined the date of each patient's first NSAIDs prescription in the study window as their 'index date'. We then divided the follow-up time after each patient's index date into successive 1-year periods until the end of the study window or the patient's death. Thus, a patient could contribute one or more of these one-year periods of potential exposure (patient-years), which formed the main units of analysis. If the time between the index date and the end of the study window was greater than a round number of years (e.g. 2 years and 6 months), we accepted the fraction of a year as a unit for analysis, as if it were a whole year. In each of the analyses that we conducted, we only analysed incident events, censoring the periods of follow-up time after the first occurrence of the outcome of interest.

Exposures

For each patient in the cohort, we calculated the number of days with current exposure to a range of medicines in the successive 1-year periods following their index date. These drugs were NSAIDs, ulcer-healing drugs, aspirin, anticoagulants, ACEIs, diuretics and also cardiovascular drugs as a combined class. We expressed these exposures as a 'percentage of days covered' for the period. We then classified the 'percentage of days covered' values for each drug group as none, low (>0% to <25%), medium (25% to <50%) or high (≥ 50%). In addition, we identified the use of these non-NSAIDs prior to the index date, and we identified patients who had undergone endoscopy (a marker for suspected GI bleeding) at some point in the study window, before or after their index date. We also included age, gender and Carstairs deprivation score as potential risk factors. Carstairs scores, derived from patients' postcodes and 1991 Census data, were divided into six categories with Category 1 being the most affluent category.[222,223]

TABLE 15 *Characteristics of 131,410 patients in the study cohort at index date (date of first NSAID use in the study window)*

Patient characteristics	
Mean study timings (years)	
Lead-in (time to index date)	2.7
Follow-up (time after index date)	4.9
Age (years)	
Mean (median)	49.7 (50)
Sex[a]	
Male	55,124
Female	76,284
Carstairs deprivation score (%)	
1	7.0
2	17.4
3	24.8
4	19.2
5	11.8
6	19.8
7	0.0
Selected history prior to index date (%)	
GI events	0.8
Endoscopy	8.5
Acute renal failure	0.1
Renal impairment	0.9

[a] Sex was not recorded for two patients.

In this way, we were able to identify exposures and factors of interest relating to each of the periods of time contributed by a patient, including exposures prior to that period, if these exposures occurred within the study window. Since the prior risk factors and the patient's age changed each time a new period began, we re-evaluated these variables on each anniversary of a patient's index date. No analyses by ethnic group were possible, because sufficient ethnicity data were not routinely collected within the NHS in Tayside at this time.

Outcomes

We defined three adverse event outcomes: a hospital admission where the primary diagnosis was an upper GI event (a disorder of the oesophagus, stomach or duodenum), such as a gastric ulcer or GI bleeding; a hospital admission where the primary diagnosis was acute renal failure; or renal impairment, which included the cases of acute renal failure but also included any patients with serum creatinine concentration ≥150 μmol/ml.

Statistical models

For each of the three outcomes of interest, we modelled the number of outcome events as Poisson variables with the logarithm of follow-up time as an offset variable. We included all risk factors as covariates in the three respective regression models in order to produce adjusted estimates of the probability of the outcome occurring. Results are presented as adjusted RRs for each risk factor. In contrast to the approach we took with the statins cohort, our emphasis here was on estimating the different levels of risk for users of the drug of interest (NSAIDs) over a number of years; we did not compare NSAIDs users with non-NSAIDs users, as the potential problems posed by NSAIDs are evidently not in dispute.[190]

We also report unadjusted rates of adverse events for men, women and older people as examples of the morbidity experience of people in the study cohort. Analyses were performed in SAS 8.

NSAIDs cohort: results

NSAIDs cohort: results. Characteristics of patients

Patient characteristics on their index dates are summarised in *Table 15*. There were 131,410 individual patients in the study cohort. They contributed in total 645,000 patient-years of follow-up time in the study window, a mean of 4.9 years per patient. As patients in Tayside had qualified for the cohort on the basis of NSAIDs use rather than diagnosis, people in the cohort ranged from children to adults aged over 90 years. The median age in the cohort was 50 years for men and 49 years for women, with a slightly larger proportion of women than men in the cohort. The age and sex distribution of the people in the cohort are shown in *Figure 8*. Female users were more common than male users in every age band. The modal age group was the 40s for both men (9880) and women (12,708). In the age groups under 50 years NSAIDs were probably more often used for back pain, discomfort from injuries and menstrual pain than for RA or OA. Very few patients had suffered a renal or definite GI event before their index date, although 8.5% had undergone an endoscopy.

In total, 928,888 prescriptions for NSAIDs were dispensed during the study window (*Table 16*). The majority (over 60%) of these were for ibuprofen, diclofenac and naproxen and, as we had anticipated, virtually all were for Cox-1 NSAIDs. We noted that some physicians had prescribed etodolac, a Cox-2 NSAID, during the study window, but as the proportion of etodolac

TABLE 16 *Distribution of NSAID prescriptions by type of NSAID in the study cohort; 1989–96*

Drug	No. of prescriptions	Percentage
All NSAIDs	928,888	100.0
Ibuprofen	230,456	24.8
Diclofenac	203,669	21.9
Naproxen	154,982	16.7
Mefanamic acid	74,961	8.1
Piroxicam	60,102	6.5
Indomethacin	39,976	4.3
Arthrotec	26,206	2.8
Ketoprofen	25,900	2.8
Fenbufen	20,318	2.2
Nabumetone	16,013	1.7
Azapropazone	15,273	1.6
Flurbiprofen	14,659	1.6
Tenoxicam	9,259	1.0
Diflunisal	8,942	1.0
Etodolac	8,830	1.0
Tiaprofenic acid	5,534	0.6
Sulindac	2,728	0.3
Other Cox-1s	11,080	1.2

TABLE 17 *Summary of drug experience of patients in the study cohort (before and after NSAIDs first prescribed)*

Drug experience	Percentage of patients
Drug exposure in lead-in period (before index date)	
Ulcer-healing drugs	9.2
Aspirin (for CVD)	3.5
Anticoagulants	0.3
ACEIs	1.2
Diuretics	8.7
Cardiovascular drugs	16.7
Drug exposure during follow-up (after first NSAID)[a]	Percentage of days covered
NSAIDs	14.2
Ulcer-healing drugs	8.1
Aspirin (for CVD)	3.8
Anticoagulants	0.5
ACEIs	1.7
Diuretics	8.6
Cardiovascular drugs	17.9

[a] All follow-up included without censoring.

prescriptions was very low (1%), we maintained the integrity of the cohort, and did not exclude patients with etodolac from the descriptive statistics or the analyses.

Exposures from drugs other than NSAIDs occurring prior to the index date, and during the follow-up period, are shown in *Table 17*. The percentage of days on cardiovascular drugs (17.9%) during the follow-up was greater than that on NSAIDs (14.2%). Since cardiovascular drugs are prescribed in the main for older people, it is probable that a high proportion of older people in the cohort took NSAIDs while being on routine cardiovascular medication.

NSAIDs cohort: results. Adverse event outcomes

Upper gastrointestinal events

There were 4834 incident GI events, 2799 in women and 2035 in men, during follow-up. Typical unadjusted GI event rates per 1000

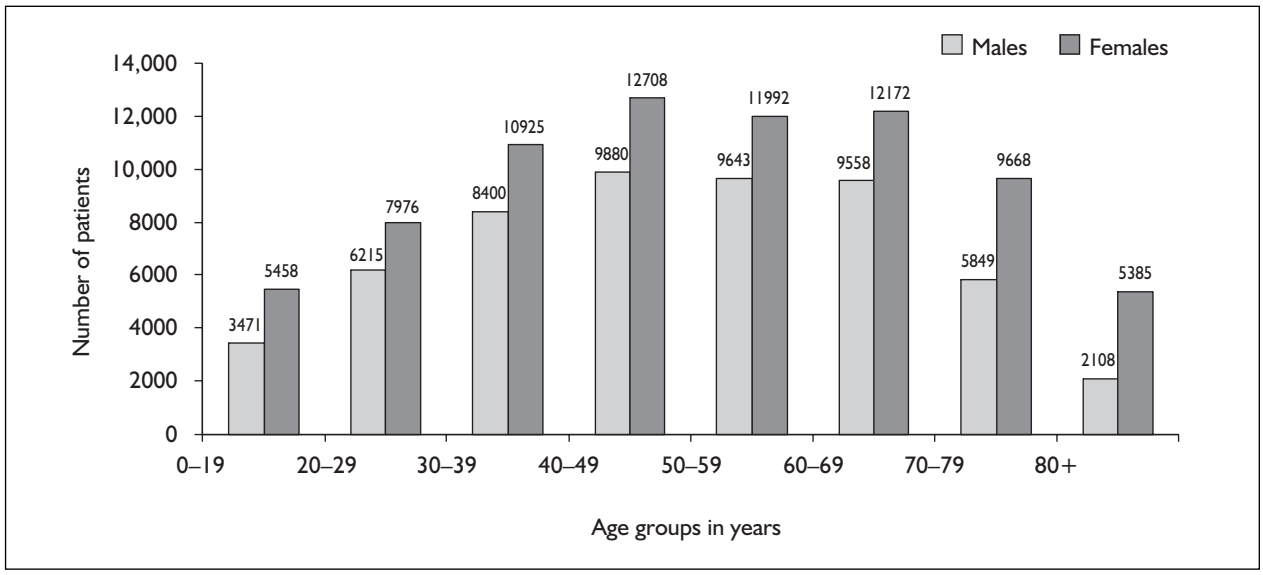


FIGURE 8 *Distribution by age and sex of patients prescribed NSAIDs for any reason in Tayside, 1989–96*

person-years were 7.41 for women, 8.05 for men and 11.02 for people aged 70–79 years. Although all of these people used NSAIDs at some point in the study window, we cannot, of course, attribute all these events to the direct effects of NSAIDs.

Nevertheless, as *Figure 9* demonstrates, current level of exposure to NSAIDs was associated with the risk of a GI event in a marked dose–response relationship. The RR for a GI event in patients with high current NSAIDs coverage was 1.48 (95% CI 1.38 to 1.60) compared with patients having no current exposure. An increasing risk with age, (independent of level of exposure to NSAIDs) was also evident, the RR for people aged 70–79 years being 1.2 (95% CI 1.09 to 1.32) compared with people in their 50s. Previous use of NSAIDs was not associated with an increased probability of a GI event.

In contrast, a history of renal impairment and a history of endoscopy were associated with increased risk. Despite the censoring of the data after each patient's first GI event, the largest apparent risk factor was exposure to ulcer-healing drugs, low coverage having an RR, compared with no coverage, of 5.08 (95% CI 4.53 to 5.7). This risk level was probably not due to a causal relationship (ulcer-drugs leading to GI events), but was perhaps a marker of treatment for early symptoms preceding the GI event for which the patient was later admitted to hospital.

Being female appeared to diminish risk. It is possible that this association was due to a behavioural pattern in women, that is, consulting at an earlier stage with symptoms arising from their medication. It is not clear why cardiovascular drugs should appear to diminish risk; again, this could possibly be a marker of consulting behaviour or of extra monitoring provided by some physicians for cardiovascular patients. Social deprivation did not appear to be an important risk factor for GI outcome.

Acute renal failure

There were 1387 incident cases of acute renal failures, 715 in women and 672 in men, during follow-up. Typical unadjusted acute renal failure rates per 1000 person-years were 1.85 for women, 2.61 for men and 3.87 for people aged 70–79 years). Although all of these people used NSAIDs at some point in the study window, we cannot attribute all these events to the direct effects of NSAIDs.

However, current level of exposure to NSAIDs was clearly associated with risk of acute renal failure in a dose–response relationship. The RR for patients with high NSAIDs coverage was 1.69 (95% CI 1.48 to 1.92) compared with unexposed patients (*Figure 10*). Previous use of NSAIDs appeared to carry a diminished risk. This may be a marker for patients who had problems with NSAIDs in the past and who had their regimen revised or stopped.

As might be expected, prior history of renal impairment was a strong independent predictor of acute renal failure (RR = 7.38, 95% CI 6.49 to 8.40). Risk also increased with age, irrespective of level of exposure to NSAIDs. For example,

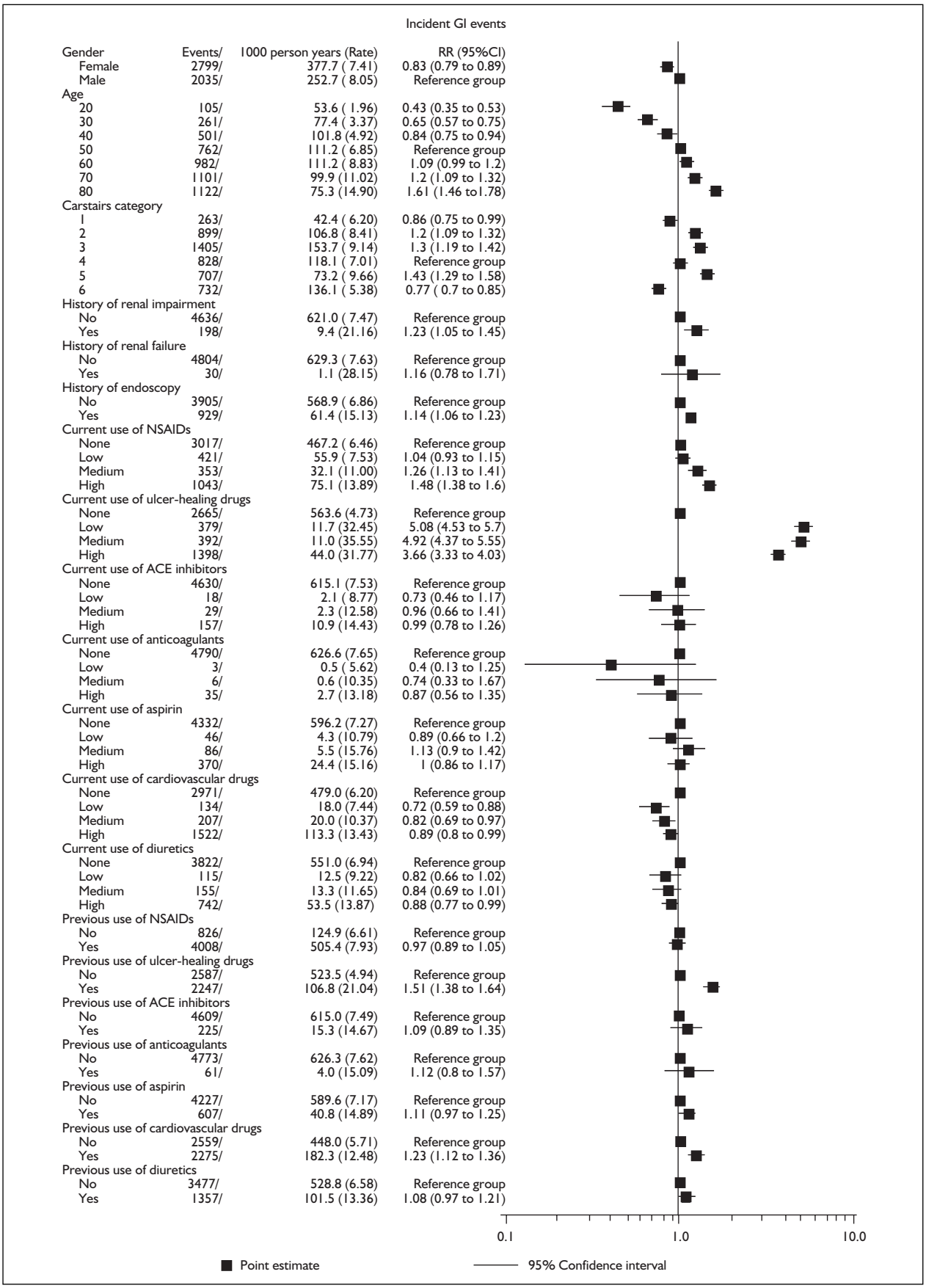


FIGURE 9 *Adjusted relative risks for incident GI events. Log scale used. RR <1.00 indicates a diminished risk relative to reference group.*

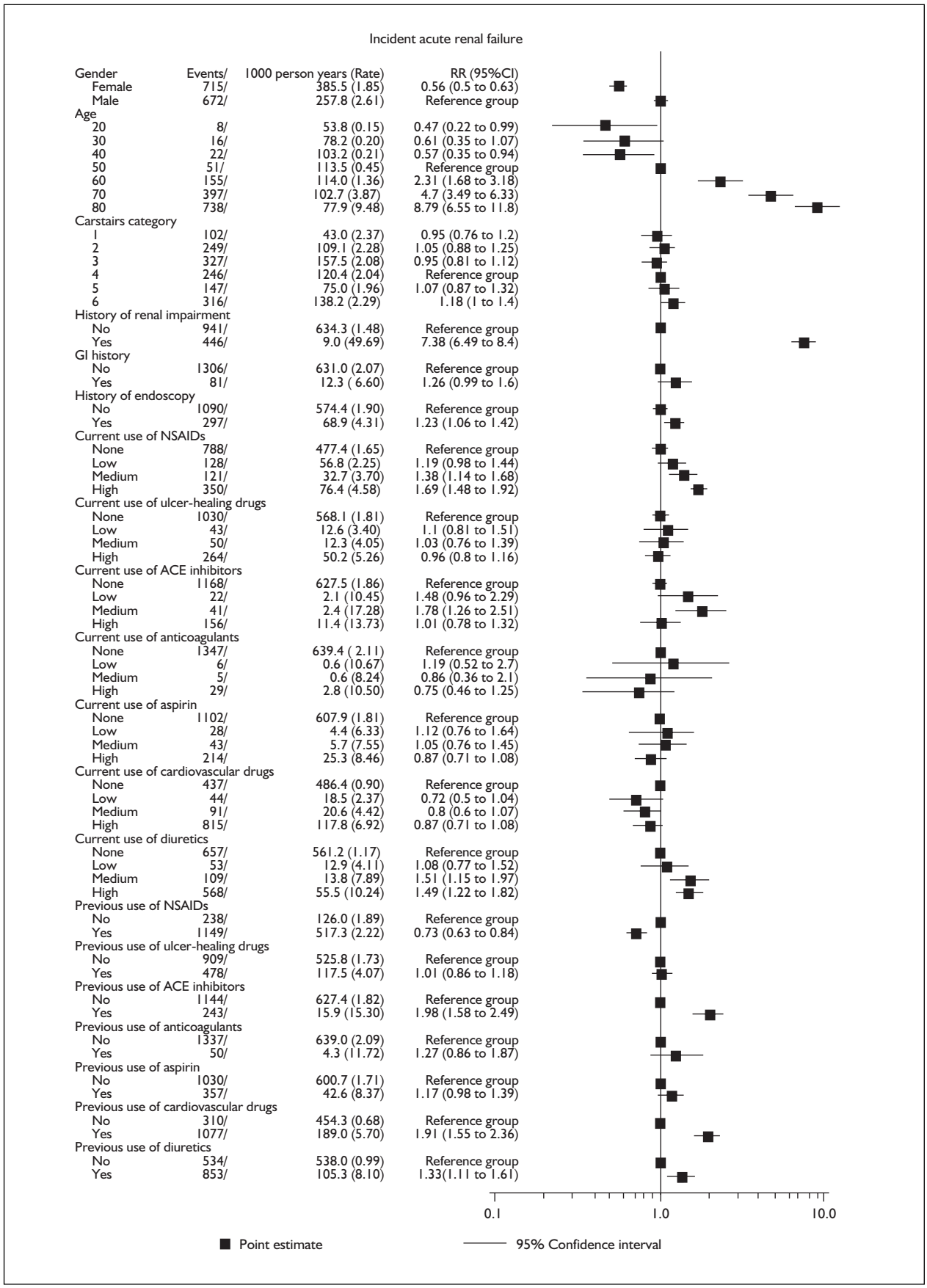


FIGURE 10 *Adjusted relative risks for incident acute renal failure. Log scale used. RR <1.00 indicates a diminished risk relative to the reference group.*

a person in their 70s carried over five times the risk of someone in their 50s. Current exposure to diuretics and ACEIs appeared to raise the level of risk. A prior history of exposure to ACEIs, cardiovascular drugs and, to a lesser extent, diuretics also carried elevated risk. Being female was associated with a diminished risk of an adverse event, as was also the case in the GI analysis.

Incident renal impairment

There were 5568 incident cases of renal impairment during follow-up, 3009 in women and 2559 in men. Typical unadjusted acute renal impairment rates per 1000 person-years were 7.93 for women, 10.11 for men and 15.51 for people aged 70–79 years. Although all of these people used NSAIDs at some point in the study window, we cannot attribute all these events to the direct effects of NSAIDs.

The pattern of associations was similar to that seen for acute renal failure. Current level of exposure to NSAIDs was associated with risk of renal impairment in a marked dose–response relationship, the risk for patients with high NSAID, coverage being 2.36 (95% CI 2.22 to 2.51) times greater than that in patients without exposure (*Figure 11*). Previous use of NSAIDs appeared to diminish risk.

An increasing risk with age (independent of the level of exposure to NSAIDs) was also clearly evident. People in their 70s, for example, had a risk nearly 20 times that of people under 30 years old. Other factors carrying an elevated risk included current or prior use of ACEIs and diuretics and prior use of anticoagulants, aspirin and cardiovascular drugs. Being female was associated with a diminished risk, as was the case with our other two outcomes of interest. Renal impairment was more probable for people in the most deprived Carstairs category in comparison with the other categories, perhaps as a result of generally worse health status in poorer people.[223]

NSAIDs cohort: *post hoc* modelling of high-risk and low-risk groups

Rationale

It is evident from our findings in this 'real-world' cohort that Cox-1 NSAIDs use was associated, in dose–response relationships, with serious adverse GI and renal outcomes. Serious adverse events were most likely to occur if the exposure to NSAIDs was in the highest category. These associations were independent of socio-demographic characteristics and other clinical variables. The analyses also confirmed that NSAIDs users with markers of susceptibility to GI problems or renal problems (prior history of GI bleeding, use of ulcer-healing drugs, endoscopy or renal impairment) were subject to additional risks of adverse events. Since NSAIDs are widely prescribed, the associated adverse events will be a relatively common part of a general hospital's case mix.

In Chapter 4 we inferred from our sample of trials that it was common practice to exclude from NSAIDs trials those patients liable to GI or renal problems (for example, patients with a prior history of GI bleeding, GI ulceration, endoscopy or renal impairment). We therefore decided to conduct a set of *post hoc* analyses. We re-analysed the cohort data to estimate the level of adverse events, which we might anticipate in NSAIDs trials that only admitted people without such conditions ('low-risk' patients). We then contrasted these results with a projection of the level of adverse events in people in the cohort who would probably have been excluded from trials because one or more of the conditions was present ('high-risk' patients). As in the main analyses, we divided up the follow-up time into 1-year periods, wherever possible, which became the main units of analysis. Each patient-year of follow-up time was assessed and then allocated to the 'low-risk; or 'high-risk' group according to the patient's current status in that period and according to their history at the beginning of that period.

Findings

The rates of GI events, acute renal failure and renal impairment in high- and low-risk patients, and in the study cohort as a whole, are plotted by sex and age group in *Figures 12–14*. These are all crude rates of events per 1000 patient-years and are not adjusted for other factors or exposures. In each graph the broken line is a plot by age group of the percentage of patients in the low-risk group, that is, those having none of the conditions which we selected for these re-analyses. The solid black line delineates the event rates in each age group for the study cohort as a whole. The lower boundary of the shaded area shows the event rate in low-risk patients by age group and the upper boundary shows the event rate in high-risk patients by age group.

The broken lines in all three pairs of diagrams indicate that low-risk patients formed the majority in this 'real world' cohort. Consequently, for each

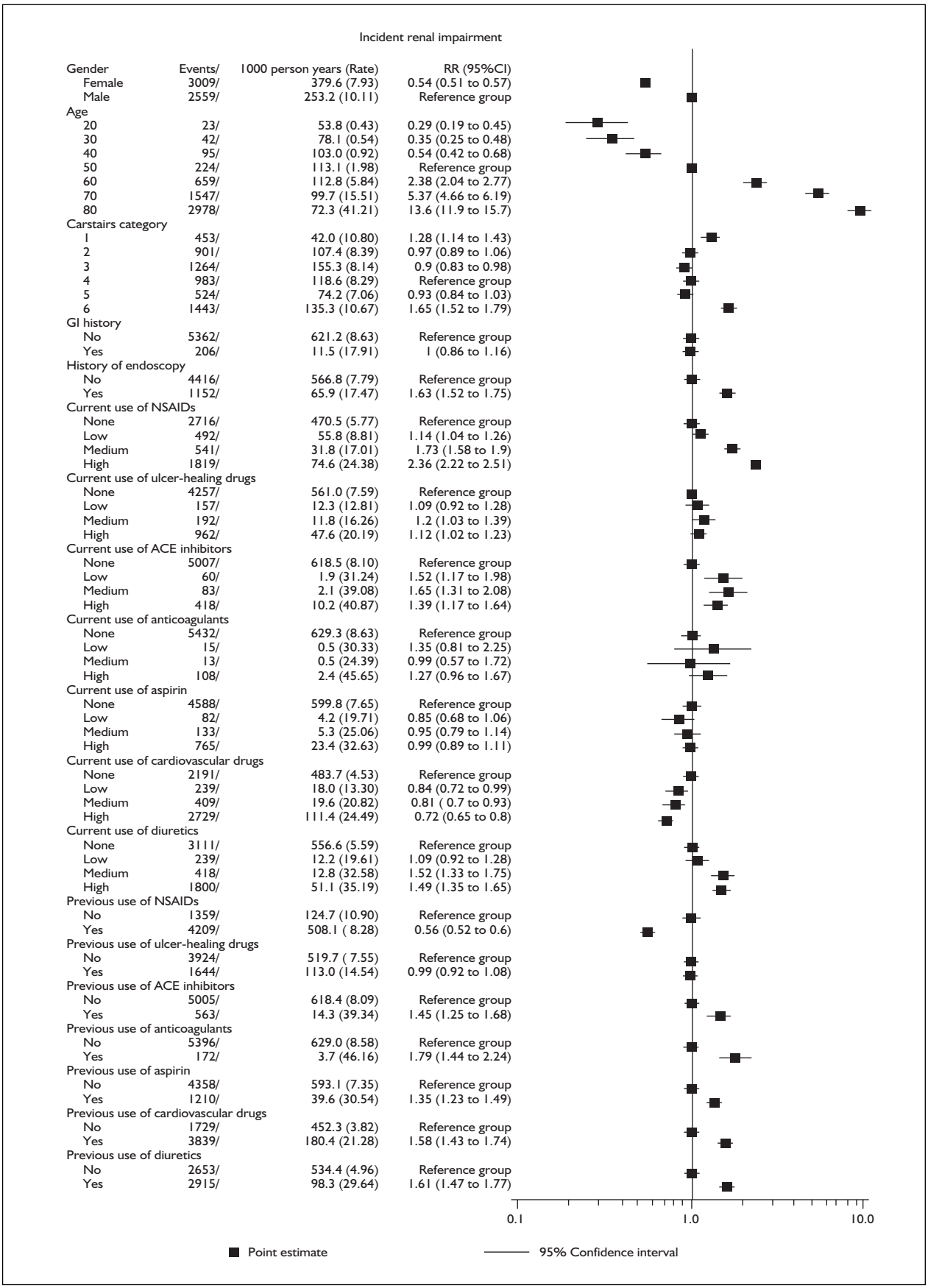


FIGURE 11 *Adjusted relative risks for incident renal impairment. Log scale used. RR <1.00 indicates a diminished risk relative to reference group.*

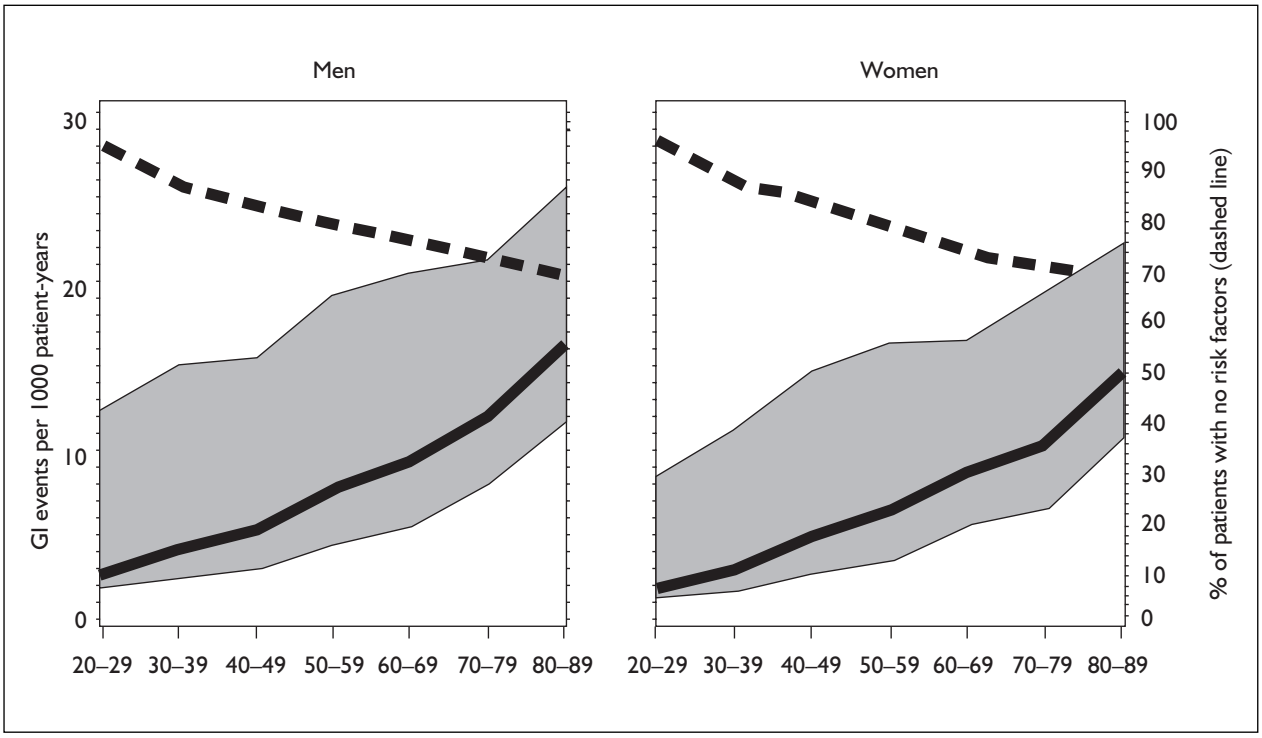


FIGURE 12 *GI event rate in study cohort (solid line) and in low- and high-risk groups (lower and higher boundaries of shaded area), and proportion of low-risk patients (dashed line); all by age group*

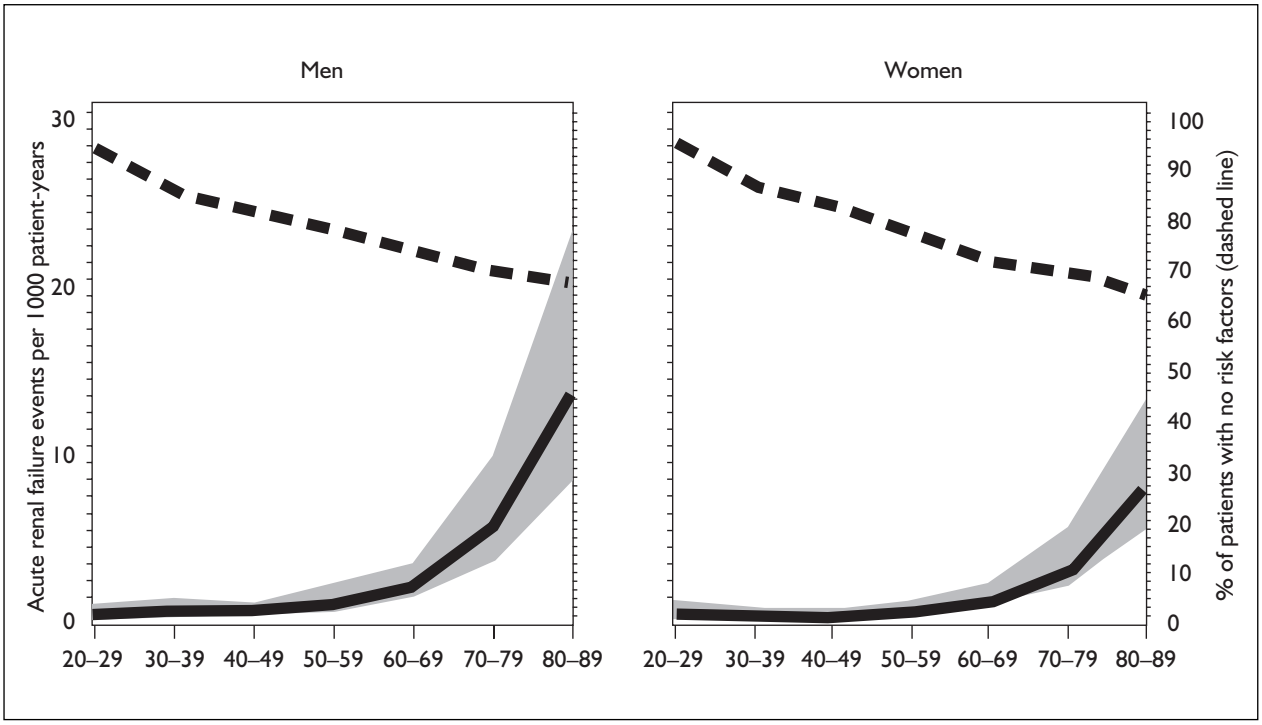


FIGURE 13 *Rate of acute renal failure in study cohort (solid line) and in low- and high-risk groups (lower and higher boundaries of shaded area), and proportion of low-risk patients (dashed line); all by age-group*

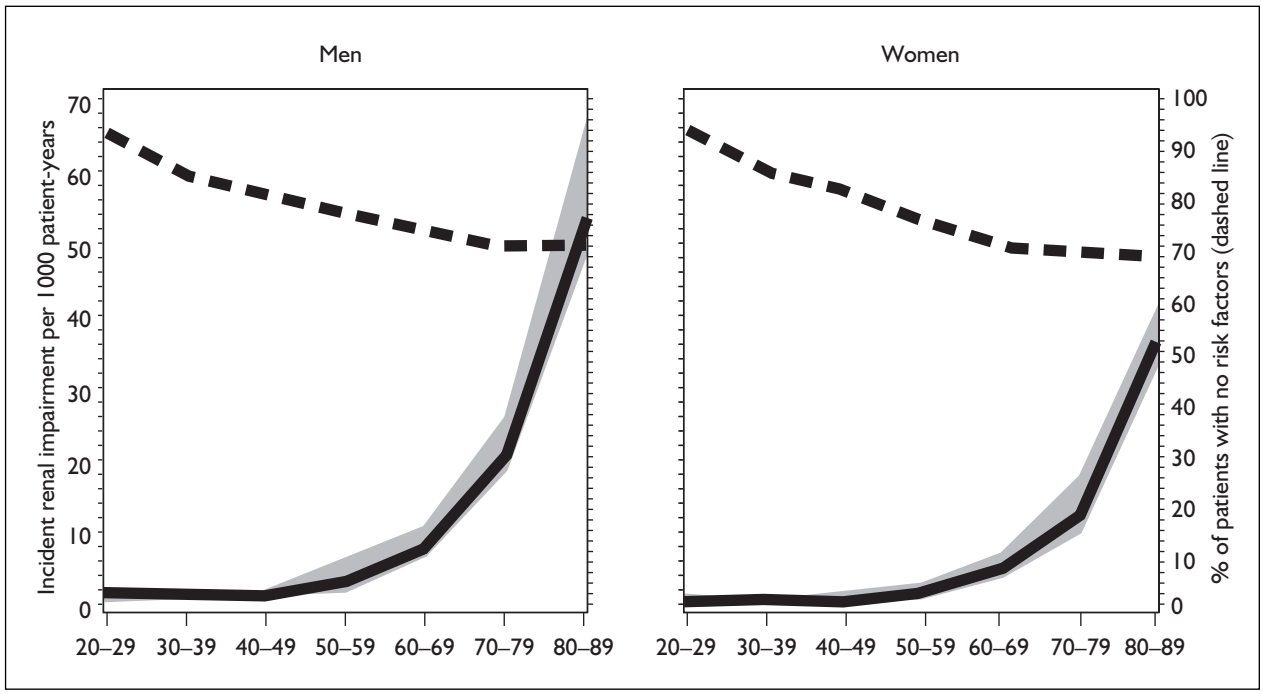


FIGURE 14 *Rate of incident renal impairment in study cohort (solid line) and in low- and high-risk groups (lower and higher boundaries of shaded area), and proportion of low-risk patients (dashed line); all by age group*

adverse outcome examined, the event rate in the study cohort as a whole (the solid black line) was closer to the lower boundary of the shaded area (the event rate in the low-risk group) than to the upper boundary. That is, the overall cohort outcomes were reasonably close to our projections of outcomes in trials. However, a closer examination of the diagrams revealed a more complex picture, particularly where the age of patients was concerned. The proportion of people in the low-risk group declined with age. About 30% of patients aged ≥60 years would not have been eligible for inclusion in a clinical trial according to the criteria we have stipulated. Adverse event rates rose markedly with age in both sexes, in the cohort as a whole, in the low-risk group and in the high-risk group. Moreover, the experience of adverse events of people in the high-risk group was somewhat removed from that of people in the low-risk group; the shaded area graphically depicts this differential. This pattern would not have been obvious in an overall trial result.

The high-risk patients had higher rates (in some subgroups, substantially higher rates) of GI complications, acute renal failure and renal impairment than those likely to be represented in clinical trials. For example, men in their 70s who were in the high-risk group had a GI event rate of 21.2 per 1000 patient-years, whereas their counterparts in the low-risk group had a rate of 8.0 per 1000 patient-years. In the same age group, the corresponding GI event rates for women were 19.4 per 1000 patient-years in the high-risk group and 6.5 per 1000 patient-years in the low-risk group. There was also a differential in terms of renal impairment rates between men in their 70s in the high-risk group (25.8 per 1000 patient-years) and their counterparts in the low-risk group (18.6). Similarly, for women in their 70s the high-risk rate was 17.6 and the low-risk rate was 9.6. In short, for both sexes GI event crude rates were overall about four times greater in the high-risk than in the low-risk group. For both sexes renal impairment crude rates were about twice as great in the high-risk as in the low-risk group.

NSAIDs cohort: discussion

Our analysis had the advantages of being conducted in a large, comprehensive cohort of people in a study window of 7 years. We used socio-demographic variables, routine pharmaceutical data and NHS event data, which had been linked using well-established techniques. We adjusted statistically for a wide range of variables, and identified marked dose–response relationships between NSAIDs use and GI and renal adverse events.

Although we did not directly examine the effects of doses of NSAIDs accumulating over periods of

more than 1 year, we did include markers of previous NSAIDs use as proxies for prior exposure. We could not measure adherence to prescribed NSAIDs, so it is conceivable that adverse events occurred at lower NSAIDs coverages than those in our analysis. Neither could we measure the use of non-prescribed medicines, and it is possible that people may have also used paracetamol or other over-the-counter analgesics, exposures which we could not detect and quantify. Even though we may have lost some exactitude in measuring exposure to NSAIDs and we did not examine interactions with other prescribed medicines, we were able to adjust for the effect of other drugs such as diuretics and ACEIs.

The cohort was extensive enough for us to conduct a set of *post hoc* analyses, contrasting adverse event rates in a high-risk group, composed of people likely to be excluded from NSAIDs trials, with those in a low-risk group of people. This approach enabled us to predict considerable disparities between adverse event rates likely to be reported in NSAIDs trials and those likely to be observed in clinical practice in a sizable minority of patients, mainly older people.

GI problems in NSAIDs users have been regularly reported in randomised trials, as our sample in Chapter 4 demonstrates. In Chapter 10, we compare these trial data with our 'real world' cohort data. In contrast, data on renal problems associated with NSAIDs use have not been so assiduously reported by trialists and it has been common practice to exclude completely from NSAIDs trials people liable to renal problems. Indeed, the risk of nephrotoxicity due to NSAIDs has featured in the literature in a number of prominent reviews and editorials[229–231] and case studies.[232–235] A very small cross-over trial[236] suggested that use of ibuprofen could quickly lead to further renal deterioration in people with mild renal failure. It is possible that the tendency of the literature to focus on adverse effects in people with less than optimum renal functioning, and the 'protectionist' approach by trialists, have led to the risk of nephrotoxicity in a large NSAIDs-medicated population being underestimated in clinical thinking.

More recently, on a much larger scale than many previous studies, Evans and colleagues[237] have conducted a case–control study of about 1800 patients in an earlier version of the MEMO database, using data for the years 1990–92. The investigators estimated that oral NSAIDs were associated with a doubling of the risk for acute renal failure. The methodology of many studies linking renal problems to use of analgesics has been shrewdly questioned by McLaughlin and colleagues,[238] but the MEMO study from 1995 and our own MEMO investigation are very robust in comparison with most of the studies that McLaughlin criticises. Both MEMO investigations had large, comprehensive samples, were based on prospectively collected prescription data (rather than on recall of medicines by patients) and made adjustment for confounding by a variety of other factors.

NSAIDs cohort: further discussion of sex differences in toxicity of NSAIDs

The finding in our sample of NSAIDs users that there was a clear sex difference in susceptibility to NSAID toxicity was unexpected (see *Figures 9–11*). Women had almost half the risk of men of suffering an adverse renal outcome (RR = for acute renal failure 0.56, 95% CI 0.5 to 0.63). With regard to GI events, the risk for women was almost one-fifth less than that for men (RR = 0.83, 95% CI 0.79 to 0.89). There are several possible explanations for this difference, which we will propose and discuss here.

Patterns of treatment and adherence

It is possible that men and women differ in their adherence to prescribed NSAIDs. It is also a possibility that men take more tablets than women. For example, if women present earlier than men in the course of a painful condition, they might take the prescribed tablets for a short time, after which symptoms subside, whereas if men presented later, they might need to take tablets for longer after prescribing. However, our statistical adjustments in the analyses meant that, in theory, the risk estimates in women were independent of extent of period of exposure to NSAIDs. One hypothetical factor we could not adjust for was the prescribing of different types of NSAID (with different potencies and toxicities) according to the age and/or sex of the patient. It is conceivable that women tended to receive less potent NSAIDs or indeed that if women experienced problems with NSAIDs, they sought medical advice at an early stage and thus avoided the end-point of an adverse event. The interpretation of our findings is complicated further by the growing body of work suggesting that men and women have different types of pain system.[239]

Confounding by indication

Another possible explanation is confounding by indication. Older men and women may be taking NSAIDs for different reasons. For example,

if women were more likely to be on the drugs because of conditions such as OA which have no systemic component, and men were more likely to be taking them for pain associated with peripheral vascular disease, with attendant higher risks of other vascular problems (including renal disease), there might be a difference in toxicity. Again, it is possible that different types of NSAID were prescribed according to the condition being managed and the prevalence of these conditions varied between men and women even before old age. It is also conceivable that 'confounding by indication' might occur if men or women were prescribed NSAIDs for back pain that was in fact not joint-related or muscular but was originating in the kidneys.

Confounding through differences in other risk factors for NSAID toxicity

NSAIDs may interact with other risk factors for both GI and renal toxicity, for example, alcohol misuse may increase the risk of NSAID gastrotoxicity.[240] It could be that the toxicity differences between men and women can be explained by differences in risk factors such as these, men being greater consumers of cigarettes and alcohol, for instance.

Although we regard all these explanations as possible, further research would be required to substantiate any of them to an acceptable degree. A final possibility is that there are underlying physiological differences between men and women which lead to different rates of GI and renal adverse events in populations consuming NSAIDs (irrespective of patient or physician behaviour) or even that a degree of difference in vulnerability to such events would be observed even in populations not consuming NSAIDs.

NSAIDs cohort: conclusions

When viewed from the perspective of the large populations that are likely to receive NSAIDs treatment, adverse GI and renal events are relatively common. In our 'real world' cohort Cox-1 NSAIDs use independently increased the risk of adverse GI and renal events in dose–response relationships. Frequency of adverse events increased with NSAID exposure, but also with age and prior GI and renal problems, irrespective of NSAIDs use. Being female seemed to diminish risk. NSAIDs users with prior GI and renal impairment had a risk level substantially greater than other NSAIDs users and tended to be older. Such high-risk people, mainly older people, are commonly excluded from clinical trials of NSAIDs, which will probably underestimate the rate of adverse events associated with NSAIDs use in this important group.

Summary: NSAIDs cohort

- We used record linkage to follow up a cohort of Cox-1 NSAIDs users in Tayside, Scotland.
- The cohort was comprised of 131,410 individuals of all ages, dispensed NSAIDs for any condition in the period 1989–96.
- We analysed the patients' exposure to NSAIDs and other drugs, and adverse event outcomes, in terms of 1-year units of time.
- The risk of a GI event increased, independently of other factors, with increasing exposure to NSAIDs, high current exposure to NSAIDs elevating the risk by about 50% compared with no current exposure.
- The risk of acute renal failure increased, independently of other factors, with increasing exposure to NSAIDs, high current exposure to NSAIDs elevating the risk by about 70% compared with no current exposure.
- The risk of renal impairment (including renal failure) increased by nearly 140% with high current NSAIDs exposure compared with no current exposure.
- The risk of adverse events increased with age, irrespective of level of NSAIDs use.
- Being female diminished the risk of adverse events, irrespective of level of NSAIDs use.
- Adverse events due to NSAIDs are probably a frequent element in the hospital case mix.
- People who are at 'high risk' in terms of clinical history are often completely excluded from NSAIDs trials.
- Adverse event rates for the 'high-risk' group in the cohort were substantially greater than for the 'low-risk' group, so trials will probably underestimate the rate of adverse events produced by NSAIDs use in populations in the 'real world', particularly in older people.

Chapter 7

Population need for treatment and prevalence of usage: statins

Statins: background and objectives

Need for treatment with statins is established for people with diagnosed cardiovascular disease.[190] In the absence of national disease registers to allow an accurate assessment of need, it is necessary to examine other routine data sources to determine population estimates of need. It is useful for planning and healthcare costing to know the total number of patients who might benefit from statins treatment and the extent to which that need is being met by prescription of statins. It can also be argued that the profile of patients in need of a given treatment should be reflected in the profile of patients in clinical trials of that treatment. Accordingly, our objectives were: to determine the number and socio-demographic profile of people in the population of England in need of treatment with lipid-regulating drugs such as statins for secondary prevention; and to determine the proportion and profile of the population in need who were receiving treatment.

Statins: methods

We wished to ascertain both the number of new cases requiring treatment with statins each year and the number of prevalent cases in the population who would benefit from such treatment. We therefore used data on hospital admissions for relevant diagnoses and data on incident angina from the most recent Morbidity Statistics from General Practice Survey 1991–92.[241] We used data from the Hospital Episode Statistics (HES) database for England to estimate the need for statins by counting the number of patients discharged from hospital with appropriate diagnoses to benefit from this therapy. These data were collected from 1 April 1999 to 31 March 2000. Data were collected for all patients discharged alive from hospital with a primary diagnosis of CHD (ICD10 codes I20–25). Population statistics from the Office for National Statistics (1999) were used to derive rates per 100,000 individuals. Data on prevalence of diagnosis of cardiovascular diseases were obtained from the current statistics from the Health Survey for England compiled by the British Heart Foundation.[242] These prevalence estimates were then applied to the English population to estimate need in the population. The situation was more complex for ethnic groups, so for the latter we referred to the percentages of people from different ethnic groups who had cardiovascular diseases, as reported in the Health Survey for England. These percentages had been age-standardised to allow comparison with the general population.[243]

To estimate the prevalence of actual usage of statins amongst patients with CHD in British settings, we drew upon five key analyses, which had been recently published. These were based on the British Regional Heart Study,[244] the Health Survey for England,[245,246] a survey conducted within the Trent Health Region[247] and data from a primary care collaboration, the Doctors' Independent Network.[248] We could not find any comparable published data describing the usage of statins by people from different ethnic groups in the UK. We also referred to the General Practice Research Database,[241] and our findings in the cardiovascular cohort from Scotland, as described in Chapter 4. For the purpose of our enquiry, we did not distinguish between prescription of statins and their actual consumption by patients, that is, we did not try to determine adherence levels.

Statins: results

Statins: results. Need for treatment in the general population

Hospital admissions

Based on hospital discharge statistics, we estimated that the total of hospital-discharged patients potentially eligible to receive statins in 2000 in England was 267,000. Total counts of discharged cases with CHD, heart failure (HF), CABG or percutaneous transluminal coronary angioplasty (PTCA) tabulated by sex, age group and discharge diagnoses and procedure codes are presented in *Table 18*. Using more limited criteria

TABLE 18 *Need for statins in England, 1999–2000: counts by diagnosis or procedure*[a]

Gender	Age group (years)	Population (000s)	CHD	HF	CABG	PTCA
Female	35–44	3,368.4	1,705	139	79	172
	45–54	3,451.0	7,102	516	422	718
	55–64	2,398.5	14,893	1,785	1,226	1,653
	65–74	2,253.2	22,738	5,853	2,089	1951
	75–84	1,601.2	20,368	11,915	833	714
	85+	737.5	8,405	9,331	22	55
Male	35–44	3,450.0	6,164	243	475	1,004
	45–54	3,446.3	22,097	1,121	2,501	3,529
	55–64	2,361.5	38,729	3,762	6,020	5,196
	65–74	1,949.9	40,955	8,705	6,457	3,806
	75–84	1,017.8	21,947	10,969	1,697	1,044
	85+	265.5	4,427	4,509	35	48
Persons	35–44	6,818.4	7,874	382	554	1,176
	45–54	6,897.2	29,209	1,640	2,923	4,247
	55–64	4,760.0	53,659	5,548	7,246	6,850
	65–74	4,203.0	63,739	14,580	8,547	5,759
	75–84	2,619.0	42,349	22,914	2,530	1,758
	85+	1,003.1	12,857	13,863	57	103
	Totals	26,300.7	209,687	58,927	21,857	1,9893

[a] Indicative conditions for statins prescribing shown in table are CHD, HF, CABG and PTCA.
Source: HES, England.

of need for statins, considering only patients discharged with a diagnosis of CHD or a procedure code of CABG or PTCA as eligible, 131,000 were in need of treatment in 2000. Alternatively, truncating need for statins to those aged <75 years gave a population need of 202,000 people per year.

Morbidity statistics from general practice: incident angina

New cases of angina arising in the population have been counted in this survey. These range from 1% per year at age 45–64 years in men to 2.7% in the age range 75–84 years. It should be noted that these estimates are markedly different from smaller *ad hoc* surveys conducted in Oxford and Southampton, which reported incidence rates around 50% and an order of magnitude lower, respectively. Applying the former incidence rates to the population at risk indicated that about 130,000 new cases of angina in women and about 140,000 in men would be expected each year (see *Table 19*).

Estimate of the number of new cases requiring treatment each year

If a strategy were adopted of treating all those discharged from hospital with relevant diagnoses and identified in general practice with new onsets of angina, a total of 537,000 new patients at all ages would require treatment each year, roughly half from hospital sources and half from general practice. If more stringent criteria of need were applied only treating those aged <75 years, these figures would fall to 391,000 patients a year requiring treatment.

Prevalence estimates: cardiovascular disease/angina

Data on prevalence of diagnosis of cardiovascular disease and angina are shown in *Table 20*. In approximate terms, women made up about 45% of the 'population with need.' This slight majority of men was largely due to cases of MI, which was twice as common amongst men as amongst women. In the need population overall, older people predominated, with about one-third being aged 65–74 years and another one-third being aged ≥75 years. The number of people within each age group varied according to sex, However. Women with need tended to be older than men with need. Approximately half of women in the need population were ≥75 years, whereas only about one-quarter of men were in this age group.

The absolute numbers in need of treatment for each diagnosis are also shown in *Table 20*. If all patients with angina, past history of MI and stroke are considered eligible for treatment, a total of 3.7 million people in England aged >35 years would be considered to need a statin, roughly one in seven of the population of this age. If more

TABLE 19 *Population need for statins: incidence of angina*

Gender	Age group (years)	Population at risk (000s)	Rate	Count
Female	35–44	3,368.4	0.04	1,347
	45–64	5,839.5	0.66	38,541
	65–74	2,253.2	1.76	39,656
	75–84	1,601.2	2.24	35,867
	85+	737.5	2.15	15,856
Total female				131,268
Total female <75				79,544
Male	35–44	3,450	0.09	3,105
	45–64	5,807.8	1.08	62,724
	65–74	1,949.9	2.25	43,873
	75–84	1,017.8	2.73	27,786
	85+	265.5	2.02	5,363
Total male				14,2851
Total male <75				10,9702

Rates from Morbidity Statistics from General Practice Survey, 1991–92.[241]

TABLE 20 *Need for statins: prevalence data from Health Survey for England, 1998*

Gender	Age (years)	Population (000s)	Angina prevalence (%)	MI prevalence (%)	Stroke prevalence (%)	Gender	Age (years)	Angina counts	MI counts	Stroke counts	Need counts
Female	35–44	3,368.4	0.4	0.3	0.6	Female	35–44	13,474	10,105	202,10	
	45–54	3,451	1.4	0.8	0.7		45–54	48,314	27,608	241,57	
	55–64	2,398.5	5.5	2.4	2.2		55–64	131,918	57,564	527,67	
	65–74	2,253.2	9.9	5.5	5		65–74	223,067	123,926	112,660	
	75+	2,338.7	17	6.5	8.8		75+	397,579	152,016	205,806	
							Total	814,351	371,219	415,600	1,601,170
							Total <75	416,772	219,203	209,794	845,769
Male	35–44	3,450	0.7	0.5	0.4	Male	35–44	24,150	10,350	13,800	
	45–54	3,446.3	2.8	2.7	1.2		45–54	96,496	93,050	41,356	
	55–64	2,361.5	10.5	8.4	3.3		55–64	247,958	198,366	77,930	
	65–74	1,949.9	15.6	11.6	6.2		65–74	304,184	226,188	120,894	
	75+	1,283.3	18.3	13.5	10.3		75+	234,844	173,246	132,180	
							Total	907,632	701,200	386,159	1,994,991
							Total <75	672,788	527,955	253,979	1,454,722

restrictive criteria were applied, excluding those >75 years, where the evidence of benefit might be considered more controversial, then 2.3 million people aged 35–74 years would be considered to need treatment, about one in 11 of the population aged >35 years.

Statins: results. Need for treatment according to ethnic groups

Bhopal and colleagues[62] and Chaturvedi[249] have recently highlighted how the prevalences of the different types of cardiovascular disease vary according to ethnic group in the UK. It might therefore be misleading to calculate and report prevalence estimates for all non-'white Europeans' in the UK. For example, as Bhopal and colleagues pointed out, frequency of CHD clearly differs between Indians, Pakistanis and Bangladeshis and so a prevalence figure for the combined 'South Asian' population, for example, conceals a varied epidemiological picture.

As *Table 21* reveals, in 1999 prevalences of angina and MI were noticeably higher among Bangladeshi men (9.9 and 7.1%, respectively) than among Pakistani men (6.7 and 6.0%) and Indian men (6.8 and 4%). CHD prevalence (angina plus MI) was higher in all these three groups than in the male population as a whole. Prevalences of angina and MI were surprisingly low amongst

TABLE 21 *Prevalence of selected cardiovascular conditions by sex and ethnic group in England, 1999: age-standardised percentages*

	Numbers surveyed	Angina (%)	MI (%)	Stroke (%)
Men				
Black Caribbean	547	1.7	0.6	3.8
Indian	626	6.8	4.0	3.3
Pakistani	620	6.7	6.0	1.9
Bangladeshi	533	9.9	7.1	2.6
Chinese	301	2.0	1.3	1.9
General population	7193	5.3	4.2	2.3
Women				
Black Caribbean	748	4.3	1.0	1.5
Indian	657	3.7	0.6	1.4
Pakistani	643	4.9	2.9	1.9
Bangladeshi	563	4.3	0.4	1.4
Chinese	361	0.8	–	0.6
General population	8715	3.9	1.8	2.1

Source: Joint Health Surveys Unit.[243]

black Caribbean men (1.7% and 0.6%, respectively). In contrast, this group had a relatively high rate of stroke. The experience of males in these ethnic groups was not mirrored in women. Most female groups had prevalence rates of CHD relatively close to that of the female population as a whole (3.9% for angina and 1.8% for MI), with Pakistani women having the highest rates (4.9 and 2.9%). The overall response rate of ethnic groups in the survey's boosted minority sample was ~60%, compared with 70% in the general population sample. It is probable that these prevalences were underestimates and subject to a number of response biases.

Statins: results. Usage of statins by CHD patients

Findings from the five analyses of prevalence of lipid-reducing treatment for CHD (MI and/or angina) are set out in *Table 22*. Although these studies did not always distinguish between statins and other lipid-lowering drugs, most CHD patients on lipid-lowering drug treatment in this period will probably have been taking statins. The prevalence of treatment in the population of people with need for secondary prevention was only moderate, however. Estimates ranged from 36% of male MI patients aged 60–75 years (as reported by Whincup and colleagues[244]) to as few as 6% of patients aged >75 years (as reported by Primatesta and Poulter[245]).

Although CHD patients tend to be older, relative youth seems to have been an important factor in determining actual prescribing, as in the British Regional Heart Study (analysed by Whincup and colleagues[244]), for instance, in which men ≥70 years were 80% less likely to receive treatment than men aged <60 years. Data for 1998 from the General Practice Research Database also showed an age gradient, though this did not take into account actual need. Rates of statins prescribing for both men and women were at their highest in the 65–74 years age group (67.5 per 1000 men and 57.0 per 1,000 women in the general practice population) but were then comparatively low in the 75–84 years age group (25.5 and 21.6, respectively, per 1000). In three of the five analyses (Whincup, Reid, DeWilde[244,246,248]) treatment was associated with time since the diagnosis was given, an association suggesting that the physicians' practices were gradually changing, with more recently diagnosed cases being started on the latest 'first-line' treatment, that is, on statins.

Whether the patients were male or female does not seem to have been an important influence on prescribing, except in the study by Hippisley-Cox and colleagues.[247] This study was confined to one region in the UK but had a large sample of CHD patients, both men and women, and utilised primary care records. There are also suggestions of other sex/gender-related biases in these family doctors' attitudes to possible CHD in women, which make these findings all the more noteworthy.

These findings in mainly English samples were broadly in accord with the pattern in the Scottish MEMO cohort, which we described in Chapter 4. The cohort was composed of 3188 Tayside

TABLE 22 *Proportion of patients needing secondary prevention for CHD and receiving lipid-lowering drugs (LLDs): UK late-1990s surveys*

Authors	Survey (year of research)	Sample description (size)	Number of people with CHD	Percentage of CHD patients on LLD (95% CI shown if reported)
Whincup *et al.*, 2002[244]	Cross-section of longitudinal British Regional Heart Study (1998–2000)	Men aged 60–75 years from Primary Care in UK (3,689)	646	29% overall 36% of MI patients 23% of angina patients LLD patients tended to be younger[a], with recent diagnosis, with revascularisation
Primatesta and Poulter, 2000[245]	Health Survey for England (1998)	Men and women aged 16+ years in private households in England (13,586)	385 ≤ 75 years 143 >75 years (with CHD, + qualifying lipid level OR on LLD treatment)	30% (95% CI 25 to 34%) ≤ 75 years 6% >75 years
Reid *et al.*, 2002[246]	Health Survey for England (1998)	Men and women aged 16+ years in private households in England (13,586)	760	19.9% (95% CI 17 to 23%) LLD patients tended to be younger[a], non-smokers, recent diagnosis, with MI (i.e. not angina only)
Hippisley-Cox *et al.*, 2001[247]	Trent Health Survey (2001)	Men and women aged 36+ years from Primary Care in Trent Region (98,137)	5891	31% of men 21% of women LLD patients tended to be younger[a], male, diabetic, hypertensive, not a current smoker
DeWilde *et al.*, 2003[248]	Doctors' Independent Network (1998)	Men and women aged 35 to 84 years from Primary Care Collaboration in Great Britain (size not reported)	30,435 (with treated CHD)	29% LLD patients tended to be younger[a], with more recent diagnosis, non-smokers, with MI or revascularisation

[a] Bias towards younger people evident even if people aged 75+ years were taken out of the account.

patients discharged with MI or after a CABG in the period 1993–96. Only 23.4% received statins at some point during the study window. Again, physicians prescribed statins to younger rather than to older people, but do not seem to have discriminated according to the sex of the patient. Prescribing for statins has clearly become more frequent in Tayside, however. Data from August 2002 from the 69 primary care practices in the Tayside 'HEARTS' collaboration, a sister project to MEMO, indicated that over half of MI patients were taking statins, although this was a select group of practices where 'best practice' was being encouraged (Sullivan F and Dougall H, Tayside Centre for General Practice, University of Dundee: personal communication, 2003).

Statins: discussion

The estimates of population need presented above are essentially complementary. The HES and morbidity survey data give an indication of the annual requirement for new statins prescriptions among people suffering acute events. Some of the

hospital events are likely to be recurrent, rather than first events, so our estimates of need will tend to be inflated by a small margin. Assuming an annual cost of statins of around £300 per year, and only accepting as in need of treatment those <75 years old, the number of new cases arising in a year will cost about £195 million to treat and the prevalent cases another £1160 million to treat. The net ingredient cost of statins to the NHS in England in 2001 was £420 million.[250] This last figure includes statins for both primary and secondary prevention.

The analysis presented here illustrates the lack of comprehensive and reliable data to estimate the level of need and should be interpreted with some caution. By using data from HES, a number of assumptions had to be made to estimate need. Although patients managed at home or in the private sector will be missed, we assume that the HES are complete and a primary diagnosis of CHD indicates need for statins. The incident angina data are also subject to some caution as *ad hoc* studies did not provide estimates comparable to those obtained from the national general practice morbidity survey. Prevalence data are likely to be more robust as it is easier to count the number of cases of angina at any point in time but less easy to identify new cases. However, the Health Survey for England only achieves a modest response rate and is subject to healthy responder bias, so may well underestimate the true need for statins treatment.

In this section, we have also presented consistent evidence from English and Scottish sources that statins for secondary prevention were not being prescribed to all CHD and cardiovascular patients who might benefit from them. The analyses that we have cited describe the situation at the end of the 1990s. The reluctance of physicians to prescribe statins for people >75 years old reflects the secondary prevention evidence base prior to the publication of the Heart Protection Study and PROSPER in 2002. Yet the tendency to prescribe statins for younger people may also be a sign of a general caution in treating older people (even those with counterparts in high-profile trials) with new drugs. Most physicians do not seem to have discriminated between men and women in the prescribing of statins. This was so despite the relatively low representation of women in the relevant trials before the Heart Protection Study. Perhaps this is an indicator that physicians, or their information sources, did not regard low inclusion levels of women in trials as likely to affect the generalisability of the trial results.

With regard to need for statins by ethnic group, this particular issue is a complex one. The prevalence of CHD varies by ethnic group and by sex within ethnic group, with most variation in men by ethnicity, so it is difficult to calculate the proportion of the 'need population' represented by people from a non-'white European' background. Such an estimate may indeed have limited value in any case. If one has to assign an overall figure one might state that, on average, people from a non-'white European' background are certainly not at a lesser risk of CHD than the rest of the population, so one should regard them, at minimum, as making up a proportion of the 'need' population similar to that in the general population, that is, about 7%. We were unable to comment on the actual usage of statins by ethnic group as published data were not available.

Summary: need for and usage of statins

- Trial samples do not necessarily reflect the socio-demographic characteristics of people who need statins or who receive statins in the 'real world'.
- To estimate need for statins for secondary prevention in England and profile people with that need, we drew upon routine sources of data such as HES, Morbidity Statistics from General Practice and the Health Survey for England.
- To estimate the actual usage of statins in England we referred to five papers which had analysed survey results from the late 1990s.
- Using broad criteria, about 267,000 discharged patients with cardiovascular disease will be eligible for statins each year; in addition, 270,000 new cases of angina, also eligible, might be expected each year in the community.
- The prevalence of cardiovascular disease is much higher, though, at 3.7 million people aged ≥35 years.
- Women constituted 45% of the overall 'population with need' but formed the majority of older people with need.
- One-third of the 'population with need' was aged 65–74 years, and one-third was ≥75 years old.
- Need varied by ethnic group and by sex within ethnic group, and so a 'need' figure for all non-'white Europeans' is, arguably, of limited value.
- Only a minority of people with CHD were being prescribed statins, probably one-third at the most.
- Younger people were more likely to be prescribed statins than older people.

Chapter 8

Population need for treatment and prevalence of usage: NSAIDs

NSAIDs: background

NSAIDs have been developed by the pharmaceutical industry for the treatment of inflammatory joint diseases, such as RA and ankylosing spondylitis. The mode of action of NSAIDs is inhibition of the production of prostaglandins (local mediators of pain and inflammation) through blocking of the cyclooxygenase enzyme system. It has recently been found that there are at least two forms of cyclooxygenase, termed Cox-1 and Cox-2.[251,252] Older NSAIDs are predominantly Cox-1 inhibitors. In addition to anti-inflammatory activity, inhibition of this enzyme leads to reduced platelet stickiness (potentially a beneficial action), loss of the mucosal barrier protection to ulceration of the GI and alteration in renal function, one result of which may be fluid retention and an increase in blood pressure.

As we have remarked in Chapter 6, the GI complications of NSAIDs use have received much attention in recent years, but other adverse effects have not been so intensively investigated. The newer, purportedly more selective Cox-2 inhibitors may not affect the GI tract or the platelets to the same degree. However, they had almost no impact on the UK market until 1999, and their utilisation remains controversial (see Appendix 5). We have deliberately omitted Cox-2 drugs from the investigation in this chapter by confining the examination to data collected before 1999.

NSAIDs have both analgesic and anti-inflammatory activity. Furthermore, most painful musculoskeletal conditions, such as sprains and strains, overuse injuries and OA, involve an element of inflammation, even though they are not primarily inflammatory diseases.[253] As more and more NSAIDs have become available, many of them launched with very effective marketing campaigns, the indications and usage of these drugs have expanded to include any painful musculoskeletal disorder. Although there is relatively little evidence to show that NSAIDs are superior to simple analgesics, such as paracetamol, in the treatment of OA,[254] they have become the standard treatment for this and other common musculoskeletal conditions. Furthermore, because of their ubiquity and analgesic properties, they have come to be used for other, non-musculoskeletal causes of pain, such as headaches and menorrhagia.

NSAIDs: objectives

For these reasons, it is difficult to undertake a formal assessment of the needs for NSAIDs usage if need is defined as 'capacity to benefit', as we do not know which patients with which of these conditions will benefit more from the use of an NSAID rather than an alternative. Therefore, we have put our main focus in this chapter on the utilisation of NSAIDs, rather than on needs. However, in order to be able to relate the data to the trial findings presented in Chapter 3, we have also attempted to determine the 'potential need' for analgesic medication in OA of the knee and/or hip in the general UK population.

Accordingly, our objectives were: to determine the prevalence of the use of analgesia for painful OA of the knee and/or hip in the UK, by analysing data from a community cohort; to examine the literature on the prevalence of painful disorders of the musculoskeletal system and the utilisation of NSAIDs for these and other disorders and to see which groups of users are most likely to be particularly susceptible to the side-effects of traditional (Cox-1) NSAIDs, by looking at the age and sex profile of users and any evidence on the presence of co-morbidities.

The present NSAIDs investigation is divided into two parts. First, we present the methods used and results of an analysis from the Somerset and Avon Survey of Health (SASH) cohort. This is a community-based study of health needs, which we have accessed to determine the prevalence and associations of analgesic use for painful OA. Second, we present the results of a literature survey designed to provide us with an overview of the prevalence of pain, particularly of musculoskeletal origin, in the community, and

NSAIDs utilisation. This is not a systematic review of all the literature, which is vast in range and extent. Rather, it was designed to provide a general overview of the situation. In the discussion and conclusions we draw the findings together and relate them to our findings from NSAIDs trials and the data obtained from the Tayside MEMO database on NSAIDs prescribing and toxicity.

NSAIDs in the SASH cohort: context

The NSAIDs trials that we have reviewed concentrated on the use of NSAIDs for pain relief in OA. The trials were composed mainly of patients with painful hip or knee OA. To be able to relate these data to population-based needs, we wanted to explore data from a community-based cohort that contained information on the prevalence of painful hips and knees and the use of medications for them. The SASH database provided that opportunity.

The SASH cohort study was developed in the University of Bristol Department of Social Medicine in 1996–97, with the help of Department of Health funding, in order to explore population-based needs for common surgical interventions including cataract surgery, hernia repairs, surgery for varicose veins and primary hip and knee joint replacements. The basic structure of the cohort and the ways in which it was investigated have been described by Eachus and colleagues.[255] In brief, the cohort was randomly sampled from 40 general practice lists, the practices being selected to provide a representative sample of urban and rural and deprived and affluent areas. The sample contains data on 26,046 people aged ≥35 years. There were 12,078 men (46.4%) and 13,968 women (53.6%), all of whom completed an initial postal screening form. Those reporting hip or knee pain were sent a second, more detailed questionnaire.

NSAIDs in the SASH cohort: data analysis

For the purposes of the present investigation we analysed responses from the following questions from the SASH survey instrument:

1. The modified 'N-HANES' question on musculoskeletal pain asked separately for knees, hips and lower back: 'During the past 12 months have you had pain in either of your knees (hips, lower back) on most days for one month or longer?' – Answer options, Yes/No.
2. A diagnostic question: 'Has a doctor ever told you that you have any of the following: osteoarthritis, rheumatism, rheumatoid arthritis, another type of arthritis?' – Answer options, Yes/No for each category. We also looked at a similar question asked about cardiovascular disease, looking for positive responses to previous stroke, heart attack, heart failure or hypertension.
3. A question on the use of medication: 'During the past 12 months have you taken prescribed tablets on most days for one month or longer in order to reduce pain in either of your knees (hips, lower back)?' – Answer options, Yes/No.

NSAIDs in the SASH cohort: results

Large proportions of respondents reported pain in the lower back (29.9%), knees (21.4%) or hips (14.3%). Pain was often reported to be present in more than one of these three sites, and the associations were statistically significant; for example, one-third of those reporting knee pain also had hip pain compared with <10% of those without knee pain (χ^2, $p < 0.001$). The reported levels of 'diagnosis' were 10.9% for OA, 4.1% for RA, 4.6% for rheumatism and 7.8% for other arthritic disorders.

We then looked in more detail at those people reporting hip or knee pain (*Tables 23* and *24*). They constituted 24.6% (95% CI 23.5 to 25.7%) of the whole sample (6416 people). In total, 1627 of these people (6.3% of the whole cohort, 95% CI 5.7 to 6.9%) reported a combination of hip and/or knee pain, together with a diagnosis of OA. This combination was nearly twice as common in women as in men (8.0% compared with 4.2%, χ^2, $p < 0.001$) and was age related up to the age of 84 years. In all, 1016 people with this combination, (3.9% of the whole cohort) reported that they had used prescribed medication for their pain. Women and men were equally likely to have taken medication, but use of prescribed analgesia was slightly more common in those aged ≥65 years than in the younger age groups. People using analgesics for hip or knee pain were more likely to report a cardiovascular problem (53.4%) than those not taking analgesics (39.3%, χ^2, $p < 0.001$).

TABLE 23 *Prevalences in entire sample of knee–hip pain, knee–hip OA (need) and knee–hip OA (treatment) in men: percentages all relate to entire sample of men in the given age range*

Age range (years)	Sample number	Percentage with KH pain	Percentage with KH + OA	Percentage both with KH OA and using prescribed analgesia
35–44	3,413	13.7	1.2	0.4
45–54	2,973	17.8	2.7	1.4
55–64	2,494	25.5	6.7	3.9
65–74	2,029	27.0	7.1	4.9
75–84	993	27.8	7.2	5.2
85+	176	27.3	4.0	2.8
All men	12,078	20.7	4.2	2.6

KH, knee–hip.

TABLE 24 *Prevalences in entire sample of knee–hip pain, knee–hip OA (need) and knee–hip OA (treatment) in women: percentages all relate to entire sample of women in the given age range*

Age-range (years)	Sample number	Percentage with KH pain	Percentage with KH + OA	Percentage both with KH OA and using prescribed analgesia
35–44	3,574	15.0	1.2	0.4
45–54	3,056	24.7	5.0	2.9
55–64	2,661	33.3	11.1	6.0
65–74	2,547	35.7	12.9	8.7
75–84	1,672	38.9	13.9	10.5
85+	458	38.4	14.2	10.9
All Women	13,968	28.0	8.0	5.1

KH, knee–hip.

NSAIDs in the SASH cohort: discussion

These data are self-report based and have not been validated. Response levels varied by question (the level was usually about nine in 10 responding), and the percentages given are the proportion of those who actually answered the particular question. This presented a problem when we combined variables (i.e. knee and/or hip pain, or knee and/or hip pain with OA diagnosis). For these combined variables we have given the percentages as proportions of the entire sample, assuming that missing data mean that the factor of interest was not present. Hence, entire sample variables tended to be conservative estimates.

The very high prevalence of reported pain in the back, knees and hips is consistent with previous surveys of the UK community (as outlined in the overview of the literature). Similarly, the higher prevalence in women and the age relationship (with an apparent reduction in the very old) were expected on the basis of previous literature. There are very few comparable data on the use of analgesics for these problems or on co-morbidities. The high levels of prescribed analgesics, particularly in older people with cardiovascular disease, is striking. Given the high utilisation of 'over-the-counter' medications including products containing ibuprofen or aspirin, this probably gives a conservative estimate of the overall use of NSAIDs in this group of people.

From these data, we would extrapolate that the use of analgesic medication for knee and/or hip OA in the UK is large, with a prevalence of around 5% of the adult population likely to be taking drugs. The highest prevalence is in women over the age of 65 years. It is likely that NSAIDs are the predominant type of analgesic used, as surveys of GPs show that they are the preferred option for prescription.[256]

These data contrast with those from the MEMO database (Chapter 6) that suggest that the most common users of NSAIDs are a younger group. We presume that this is because of the high

utilisation of NSAIDs for other conditions such as back pain, soft tissue injuries and menorrhagia, which occur in younger age groups.

NSAIDs literature: epidemiology of pain

Overall prevalence of chronic pain

Pain is common. A relatively recent study of the prevalence of chronic pain in the UK community makes this clear.[257] The authors undertook a postal questionnaire survey of 5036 people aged ≥25 years, randomly selected from GP lists, in the Grampian region. There were a number of exclusions so questionnaires were finally sent to 4611 people, and 3605 forms were returned (82.3%). In all, 50.4% of respondents reported chronic pain. This varied by age and sex, and a variety of conditions were responsible, as shown in *Table 25*, with musculoskeletal conditions predominating, and being responsible for about one-third of all chronic pain reported.

Pain severity was graded on a four-point scale; 48.7% reported pain of the mildest level (Grade 1), but more severe pain was also common, with 11.1% reporting Grade 3 and 15.8% Grade 4 pain. This study also looked at treatment sought for pain by this group, including 'recent' or 'often' use of painkillers. The data are presented in aggregate form, making it difficult to understand the number answering positively to the specific questions about use of painkillers. However, it is apparent that the majority of those reporting chronic pain also expressed need for treatment, and that there was a high level of utilisation of painkillers and other forms of help, 28% expressing the highest level of need for treatment. Age and sex both affected the level of expressed need, which was significantly greater in women than in men and was higher in older than in younger people. An analogous study in Canada[258] found that only 42% of the population were not in pain.

Generalised musculoskeletal pain

The Elliott study[257] concentrated on chronic pain and allowed people to choose between a variety of causes, such as back pain and arthritis. However, generalised pain in the musculoskeletal system is common without arthritis, and is mostly classified as fibromyalgia. This is now a huge, worldwide problem.[259] Croft and colleagues found high levels of chronic musculoskeletal pain of the fibromyalgic type in Cheshire,[260] with an overall prevalence of 11.2%, a female-to-male ratio of about 2:1 and the highest levels in the 55–64 years age group. We have not been able to find any UK data on the use of drugs by fibromyalgia sufferers, but a USA study indicates that 91% were NSAIDs users.[261]

TABLE 25 *Self-reported chronic back pain or pain from arthritis in men and women and in different age groups*

	Back pain (%)	Arthritis (%)
Men	14.9	13.7
Women	17.0	17.8
Age 25–35 years	11.9	1.1
Age 35–44 years	16.5	4.9
Age 45–54 years	17.6	12.4
Age 55–64 years	18.5	20.2
Age 65–74 years	15.3	25.8
Age >74 years	15.4	28.1

Source: Elliott *et al.*, 1999.[257]

Localised musculoskeletal pain

The prevalence of localised, regional musculoskeletal pain (as opposed to generalised pain) has also been investigated. In a review of the literature, Linaker and colleagues[262] divide regional musculoskeletal pain into three main categories: back and neck pain, sprains and strains, and rheumatism/arthritis. They report that back pain is the commonest type, peaking in the age range 45–54 years, that sprains and strains predominate in younger adults and that rheumatism/arthritis is the commonest category reported by older people.

Knee pain

The knee is the commonest non-spinal site for reported musculoskeletal pain. McAlindon and colleagues[263] and O'Reilly and colleagues[264] have reported community-based data on its prevalence. Some 25% of all adults report knee pain. Knee pain is more common in women than in men and, up to the age of about 80 years, in older than younger people. Altman and colleagues[265] reported that most of this knee pain is ascribed to OA. As noted previously, NSAIDs are generally considered the treatment of choice for OA by primary care physicians in the UK, and are widely prescribed. Comparable data for hip pain are more difficult to find.

NSAIDs literature: NSAIDs utilisation

UK prescribing

Data on the prescribing of NSAIDs in the UK is available on the Prescription Pricing Authority website.[266] At the end of 2001, prescriptions of

drugs classified as being for 'musculoskeletal and joint disease' accounted for 4.7% of all prescriptions, at an estimated cost of £231.4 million. Most of these prescriptions and costs relate to NSAIDs. The leading agents used are diclofenac, naproxen and ibuprofen. Since 2001 there has been a significant increase in overall costs of NSAIDs following the introduction of the more expensive Cox-2 inhibitors.

Analgesics other than NSAIDs are widely used for musculoskeletal pain. The BNF and Prescription Pricing Authority[266] classify them as central nervous system drugs. The Prescription Pricing Authority reports that these have shown rapid growth in prescribing in recent years, with 44 million items prescribed in 2001. Co-proxamol (widely used for musculoskeletal pain) and paracetamol are the leading agents prescribed. In addition, there is, of course, extensive use of many types of 'over-the-counter' analgesics and NSAIDs (systemic ibuprofen and topical agents). We have been unable to find figures on volume of sales for these agents.

Patterns of use

We have not been able to find UK community-based data on the utilisation of NSAIDs, but some fascinating self-report data are available from the USA, Canada and France.

In France, surveys of users show that the main stated reasons for using NSAIDs are OA (34%), inflammatory arthritis (7.4%) and 'other' (58.6%).[267] People reported that they used NSAIDs erratically and on demand rather than continuously, with an average of 61 days' use out of the 270 days in the study period. NSAIDs users with OA had an average age of 62.7 years, but the other users were much younger with an average age of 45 years. In the USA, the large 1980s Physician's Health Study of male American doctors[268] looked at the usage of NSAIDs. In all, 46.4% of the 22,069 men involved reported intermittent use of NSAIDs (1–60 days per annum) and 5.7% were regular users (>60 days per annum). Users of NSAIDs tended to be heavier and have more hypertension and diabetes than non-users. A similar study in Canada in the 1990s[258] found that 21.4% of the general population reported regular use of NSAIDs, the main drugs involved being diclofenac, naproxen and ibuprofen.

NSAIDs literature: discussion

The literature on pain, analgesia and NSAIDs is huge. We did not attempt a systematic review of this literature to answer a specific question. Rather, we undertook an overview of the current knowledge on the prevalence of painful conditions and the utilisation of NSAIDs for them. However, the literature that we have found on the prevalence of musculoskeletal pain is both internally consistent and in line with our findings from the SASH study. Given that, we feel confident about our conclusions on the prevalence of painful conditions that are likely to result in NSAIDs use.

The data on the utilisation of NSAIDs are less clear. It is clear from the Prescription Pricing Authority data that many prescriptions are written for these drugs, but these data do not tell us why. We did not find publications from the UK describing the overall utilisation of these drugs. The data that we have cited from France, Canada and the USA are internally consistent, and suggest that there is a high level of population consumption, but that most people use NSAIDs intermittently and largely 'on demand' rather than on a regular basis.

The MEMO data on side-effects are based on the way in which people are actually using the drugs in the community. If, as the French, Canadian and American data suggest, most people are using the drugs on demand and intermittently, then trial results may not reflect what happens in the 'real world'. It may be that trialists need to rethink the design of trials for symptomatic drugs, and anchor them more clearly to the likely way in which people are known to use the drugs, rather than stipulating an artificial pattern of consumption.

NSAIDs: conclusion

NSAIDs were produced for the treatment of inflammatory joint diseases such as RA, but have become the standard pharmaceutical agents used in the treatment of OA, in spite of a paucity of evidence to suggest their superiority over other drugs. Their use has also spread to other painful conditions. This made a formal needs assessment (based on capacity to benefit) difficult to perform. In this chapter we have described the analysis of data from a community cohort, undertaken to estimate the prevalence of the use of analgesic medication for painful hip and/or knee OA, and an examination of the literature to estimate the prevalence of painful disorders of the musculoskeletal system for which NSAIDs might be used, and to assess their overall level of utilisation. We have also attempted to assess which

groups of users might be most susceptible to toxic side-effects from NSAIDs.

Summary: NSAIDs findings

- Data from the large population-based cohort showed that 6.3% of adults over the age of 35 years reported current hip and/or knee pain, and 3.9% of the whole cohort reported taking analgesic medication for this problem. It is likely that the majority of these people were suffering from OA.
- Those people reporting that they use analgesic medication for hip and/or knee pain were older adults, there were more women than men and they were more likely to report the presence of cardiovascular disease than those not taking medication.
- Literature on the prescribing habits of GPs suggest that it is likely that the majority of these people are given NSAIDs as their analgesic medication.
- Given the additional widespread use of 'over-the-counter' NSAIDs, we conclude that some 5% of the UK adult population are using NSAIDs for painful hip and/or knee OA, and that many of those people are at high risk of toxicity because of age and concomitant cardiovascular disease.
- Recent UK-based surveys suggest that about 50% of adults report some form of chronic pain, and that musculoskeletal disorders are the predominant cause. The majority of those in chronic pain report seeking treatment, including analgesic medication, for this pain.
- Fibromyalgia is one of the main causes of chronic musculoskeletal pain. NSAIDs are widely used in this disorder. Back pain and local soft tissue problems (sprains and strains) are also common causes of pain and the utilisation of NSAIDs.
- Users of NSAIDs for fibromyalgia, back pain and regional soft tissue disorders are generally younger than users with OA. Data on co-morbidities that might affect toxicity are not available in these NSAIDs users.
- Data from the Prescription Pricing Authority show that NSAIDs account for 4.7% of UK prescriptions, at an annual cost to the NHS of over £200 million. Naproxen, diclofenac and ibuprofen are the most commonly prescribed agents. Over-the-counter use of NSAIDs is also common, but no figures are available.
- Data from France and North America show that 20–40% of the adult population report the use of NSAIDs, but that the majority of this use is intermittent rather than regular. OA is one of the main reported reasons for the utilisation of NSAIDs.
- People who use NSAIDs for OA in the 'real world' are slightly younger than people in the relevant trials, but the proportion of women in trials and in the 'real world' are similar.
- Actual patterns of consumption of NSAIDs for OA and other disorders differ greatly from the pattern of utilisation imposed by investigators in clinical trials.

Chapter 9

Disparities between trial samples, need populations and treated populations: statins

Statins: background and objectives

In Chapters 3–8, we delineated with respect to our exemplar drugs, statins and NSAIDs, the socio-demographic profiles of people in trial samples, in populations 'with need' and in populations 'on treatment'. Our next objectives were to present a synopsis of these profiles and of outcomes in the different samples and populations and to suggest explanations for any disparities between the profiles.

Statins: methods

We drew upon principal data from preceding chapters and summarised them graphically. With regard to the analyses of English Surveys of prevalent CHD cited in Chapter 7, data pertinent for comparative purposes (i.e. prevalence figures for a mixed-sex sample) were only available in the papers by Primatesta and Poulter,[245] Hippisley-Cox and colleagues[247] and DeWilde and colleagues.[248] We also present data taken by us from the Health Survey for England.[242,243] Treatment data from these sources were usually based on use of any lipid-lowering drug (LLD), which we have accepted as a reasonable proxy for use of statins. Blank spaces in graphs indicate that pertinent or usable data were not available. Statins need and use data were from English populations, with the exception of data from DeWilde and colleagues, which were from England, Scotland and Wales, and data from MEMO, which were from a Scottish population.

Statins: results

Women

The set of bar-charts in *Figure 15* gives a general overview of the situation relating to CHD at the end of the 1990s. There are a number of salient features. Women constituted 38–47% of the populations with need for treatment, and formed slightly smaller proportions of the populations actually on treatment with LLDs (*Figure 15a*). Most studies, however, reported that sex was not an independent determinant of whether lipid medication was prescribed. However, in comparison with need and usage levels, women were clearly underrepresented in secondary prevention trials, on average only contributing 16% of trial samples.

Older people

It was difficult to extract statistics describing the age profile of samples and populations which were directly comparable with each other. The average age for need tended to be in the mid to late 60s, whereas the MEMO 'on treatment' population had an average age of about 60 years, which was similar to the average age in trials (*Figure 15b*). About two-thirds of the English population with need were aged ≥65 years, but treatment was probably given to only a half of those with need in this age group. In trials, people ≥65 years old were very much a minority, constituting (where figures were available) an average of about one-fifth of trial participants (*Figure 15c*).

Ethnic groups

Ethnicity was poorly reported in trials, was not reported at all in UK trials and was not a prominent issue in our data sources for patterns of need and treatment (*Figure 15d*). Health Survey for England data did show, however, that levels of cardiovascular need varied across ethnic groups and by sex within ethnic group, although even these levels were probably underestimates. The prevalence of CHD was about 80% greater in Bangladeshi men than in the general male population of England, for example. This complex epidemiological picture cannot be addressed within the scope of our present study. As an expedient, we have denoted the proportion formed by non-'white European' people in the need population as being approximately commensurate with their proportion in the general population.

Statins: discussion

The socio-demographic profiles of statins trials clearly did not reflect the population with need, (at least when judged by English standards),

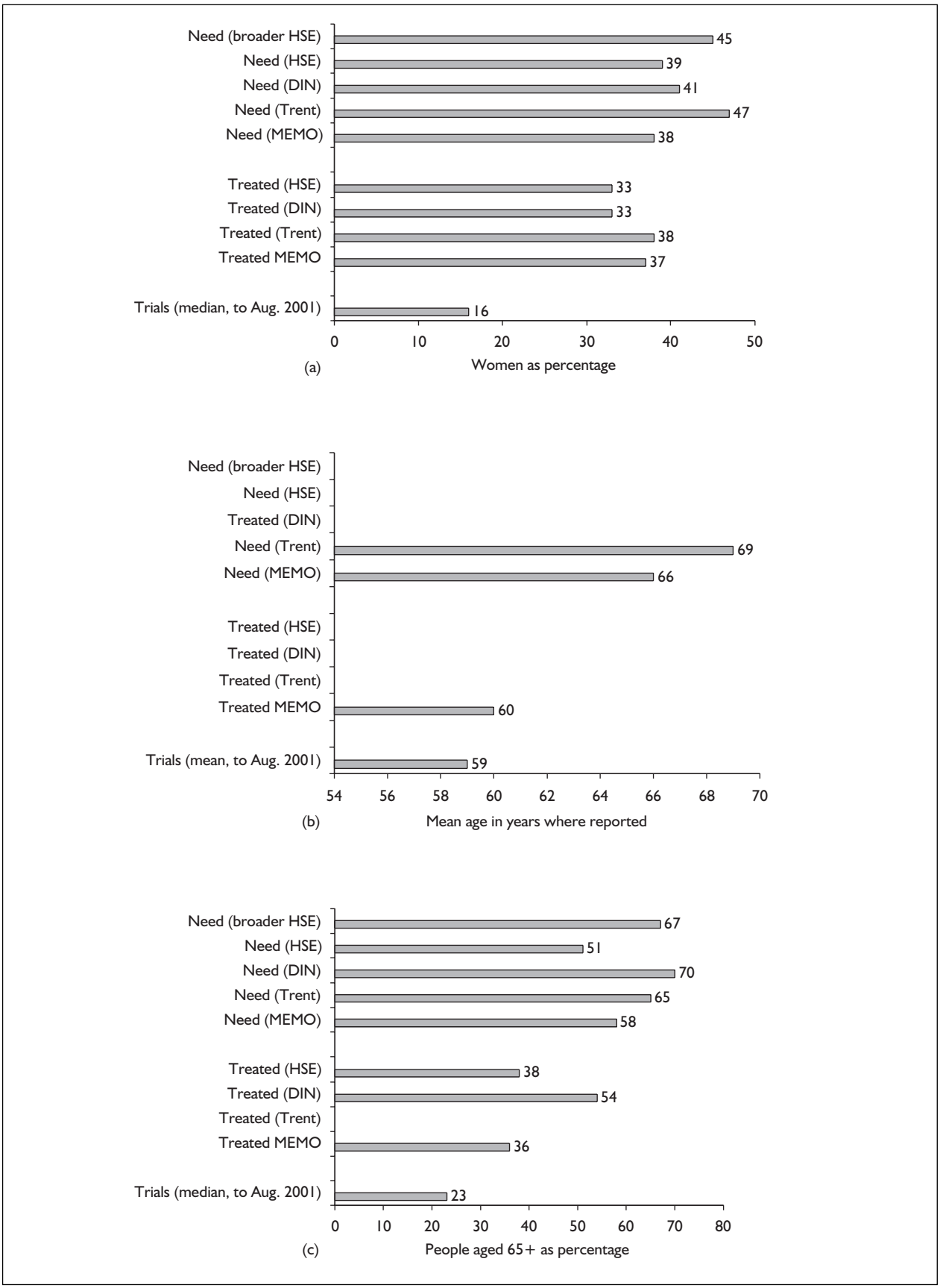
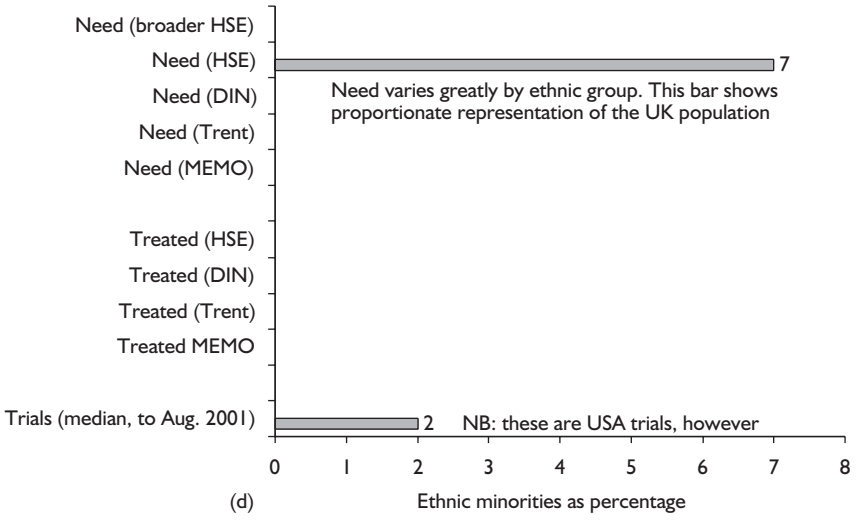


FIGURE 15 *(a) Women as a percentage of statins samples; (b) mean age of statins samples (years); (c) people aged 65+ years as a percentage of statins samples; (d) ethnic groups (other than white European) as a percentage of statins samples; (e) key to statins samples, with age range (diagnostic eligibility criteria)*



Need (broader HSE)	Taken by us from Health Survey for England 1998, age 35+ (angina, MI or stroke)
Need (HSE)	Health survey for England 1998, ages 16–75 Primatesta and Poulter, 2000[245] (CHD) (ethnicity estimate from health of minority ethnic groups)
Need (DIN)	Doctors' Independent Network, ages 35–84 DeWilde *et al.*, 2003[248] (CHD)
Need (Trent)	Trent Survey, ages 35+ Hippisley-Cox *et al.*, 2001[247] (CHD)
Need (MEMO)	MEMO database, 1993–96, ages 35+ (post-MI or -CABG discharge)
Treated (HSE)	Health Survey for England 1998, ages 16–75 Primatesta and Poulter, 2000[245] (on LLDs for CHD)
Treated (DIN)	Doctors' Independent Network, ages 35–84 DeWilde *et al.*, 2003[248] (statins for CHD)
Treated (Trent)	Trent Survey, ages 35+ Hippisley-Cox *et al.*, 2001[247] (on lipid-lowering drugs for CHD)
Treated (MEMO)	MEMO database, 1993–96, ages 35+ (on statins post-MI or -CABG discharge)
Trials (to August 2001)	Statins trials to August 2001, mostly aged <65 (mainly CHD, occasionally other CVD)

FIGURE 15 *(cont'd)*

although some later trials, Heart Protection Study and PROSPER, corrected the age and sex imbalance to a large degree. We discussed in Chapter 2 some justifications offered by trialists for the deliberate construction of samples, in which women, older people and ethnic groups are underrepresented. One major justification would be the goal of creating a manageable and relatively homogeneous sample, which would produce unambiguous and statistically precise results. A further argument that trialists might offer would be the 'protectionist' one that older people should not be in trials of a drug before its effectiveness and safety have been established in younger people. (A younger sample would, by default, entail a greater proportion of men as CHD appears at a younger age in men compared with women.) It was necessary, this line of

argument might continue, that the Heart Protection Study and PROSPER were undertaken but appropriate that they came at the end of the experimental history of statins.

We observed in Chapter 7 that only about one-third of people with CHD were being prescribed lipid-lowering drugs in the late 1990s. It lay outside the scope of our present study, however, to determine in detail why the socio-demographic profile of the population on treatment took its particular shape and what influences were acting on the prescribing practice of physicians. Indeed, this slow diffusion of a new treatment is not likely to be peculiar to statins. Whatever influences were at work, the outcome was that physicians seem to have adhered closely to trial results with regard to age, preferring to prescribe for younger people. If anything, they may have erred on the side of caution, even in patients before the age of 75 years, perhaps owing to anxiety about prescribing a new drug in older people even though peers of the latter had been included in clinical trials.

With regard to sex, underrepresentation of women in trials does not seem to have been construed as a reason to discriminate against them in the prescription of statins. We might posit a number of explanations (which are not mutually exclusive) for this: it was a matter of fairness to allow younger women the potential benefits of this new drug; prescribing for younger women was considered a low-risk strategy, because women had been represented to some degree in relevant secondary prevention trials (and in primary prevention trials) without any apparent ill-effects; the 'average' therapeutic effect seen in samples of men and women was likely to be generalisable to women even if they had formed a minority in trials. Results from later trials and from our evidence syntheses reported in detail in Chapter 11, justified the practice of physicians (or at least the influences acting upon them) with regard to women, although statins were also shown to be effective in older people. We estimated from four large secondary prevention trials that statins, compared with placebo, reduced the risk of coronary events by about 25% in both men and women and in people aged 65–75 years, and also in people <65 years old.

Statins are an example of a highly effective class of drug, likely to benefit large sections of society. (However, we have also explored some of our reservations about the evidence base with regard to the possibility of adverse events in different socio-demographic groups, especially in older people and people in advanced old age, in Chapter 11.) With less effective or more risky drugs, particular care would need to be taken in evaluating the balance of harm and benefit in older people.

Statins: conclusions

Although not all people with CHD who might have benefited from statins were receiving them, women made up broadly similar proportions of both the 'with need' and the 'on treatment' populations. From the perspective of need, the bias was towards underrepresentation of women in trials, however. Older people, despite their level of need, tended to be underrepresented in the 'on treatment' populations and in trials. We could not discern whether UK ethnic groups were represented in UK trials according to their needs or were being treated according to their needs.

Summary: disparity in statins samples and populations

- For statins for secondary prevention of CHD, we compared the socio-demographic profiles of trial samples of the 'with need' populations and of the 'on treatment' populations.
- Women made up 40–45% of the 'with need' populations and almost the same proportion of the 'on treatment' populations.
- However, in comparison with need and treatment levels, women were under-represented in trials until late in the history of statins.
- Older people, aged ≥65 years, made up nearly two-thirds of the 'with need' populations, but only half of this group were receiving treatment with statins.
- Only about one-fifth of people in trials were aged ≥65 years.
- Some non-'white European' groups in the UK have high prevalences of CHD.
- But their levels of treatment and involvement in trials were not clear from a UK perspective.
- For whatever reasons, when prescribing, physicians followed the profile of trial samples with regard to the low representation of older people in trials, but not with regard to the low representation of women in trials.

Chapter 10

Disparities between trial samples, need populations and treated populations: NSAIDs

NSAIDs: methods

We drew upon principal data from Chapters 4–8 and tabulated them. Our sources of data were more limited in number than with statins. Our sample of trials of NSAIDs for people with OA provided data on characteristics of patients and on adverse outcomes, whereas the SASH[255] provided cross-sectional data on people with OA who used analgesia (not necessarily NSAIDs) or who might have a potential need for it, but SASH could not provide outcome data. The MEMO cohort furnished details of patient characteristics and outcomes for prescribed NSAIDs users. These MEMO data did not discriminate between people prescribed NSAIDs for OA and those, particularly younger people, prescribed NSAIDs for other conditions, such as back pain or injuries. However, these cohort data were valuable for providing robust estimates of how adverse outcomes with NSAIDs varied by sex, age and exposure. Blank spaces in tables indicate that appropriate or usable data were not available.

NSAIDs: results

Women

As *Table 26* shows, women formed the majority, about two-thirds, of those who potentially might use analgesia for knee and/or hip OA (the population 'with potential need') and about two-thirds of those who did in fact use analgesia (the population 'on treatment'). From this perspective, women were appropriately represented in trials of NSAIDs for OA. Women formed the majority in MEMO but were not as large a proportion in MEMO as they were in trials or in SASH.

Older people

Users of analgesia for knee and/or hip OA tended to be relatively old, with 59% of them being aged ≥65 years (*Table 26*). We therefore expected the mean age in trials to be >65 years whereas it was in fact less, at 62 years. MEMO patients were slightly younger than trial patients and SASH participants, because the MEMO cohort included all NSAIDs users, regardless of their diagnosis.

Ethnic groups

SASH could not tell us about the ethnic profile of people with OA or of people who used analgesia for OA. Neither were UK trials informative in this respect. Three of the four trials reporting on the ethnic profiles of their samples were USA trials.

Outcomes

As *Table 27* shows, our sample of trials revealed very little about how adverse event outcomes varied according to the socio-demographic

TABLE 26 *Socio-demographic characteristics of NSAIDs samples*

	People in NSAIDs trials for OA (mainly knee and/or hip OA)	Users of analgesia for knee and/or hip OA (from SASH)	Any people with knee and/or hip OA (from SASH)	On NSAIDs treatment in MEMO cohort: not necessarily OA diagnosis
Median proportion women (%)	69	69	69	58
Mean age (years)	62	Not known	Not known	50
Proportion aged 65+ years (%)	Not known	59	52	66 (60+ years)
Proportion of ethnic minority (%)	13 (median from 4 trials, but 3 were in USA)	Not known	Not known	Not known

TABLE 27 *Cox-1 NSAIDs: adverse GI outcomes in trials and in MEMO cohort (rates per 1000 patients in trials and per 1000 patient-years in MEMO cohort)*

	NSAIDs trials for OA patients on NSAIDs (mainly knee and/or hip OA)	**NSAIDs trials for OA patients on placebo (mainly knee and/or hip OA)**	**Patients on NSAIDs in MEMO cohort (any diagnosis)**
Rate of GI events (median values in trials)	7.3 Ulcers 21.1 GI bleeds 39.2 GI Drop-outs	0 ulcers 16.9 GI bleeds 10.5 GI drop-outs	7.7 upper GI events
Excess risk of GI events in men compared with women	Not clear	Not clear	+12% (adjusted)
Excess risk of GI events in older compared with younger people	Not clear	Not clear	+20% for people 70–79 years +61% for people 80+ years (adjusted and compared with people 50–59 years)
Excess risk of GI events with higher coverage/doses of NSAIDs	Not clear	Not applicable	+26% for medium coverage[a] +48% for high coverage[b] (adjusted and compared with no current NSAID use)

[a] Medium coverage was defined as from 25% to <50% of days in the 1-year period being covered by an NSAID prescription.
[b] High coverage was defined as ≥ 50% of days in the 1-year period being covered by an NSAID prescription.

characteristics of people in the samples. It was notable, however, that the trials reported a higher average level of GI events than were observed in the 'real world' MEMO cohort. For example, the median rate of GI bleeds was 21.1 per 1000 patients in the trials, whereas the rate of upper GI events in the MEMO cohort was 7.7 per 1000 patient-years. There are a number of possible reasons for this incongruity. The MEMO cohort was, on average, younger than the trial samples and so would have been less liable to adverse events. Furthermore, in MEMO we only classified events in the upper GI tract (oesophagus, stomach and duodenum) as adverse events. These events were identified through contact with a hospital for investigation or treatment, whereas as far as can be discerned from their protocols, most trials would have captured even relatively mild events in all parts of the GI system, based on reports from the participants. However, it was the MEMO cohort that demonstrated how the risk of adverse GI events was greater for men than for women, and that risk increased with age and with length of period on NSAIDs for people of both sexes.

The trials were even less informative in respect of acute renal failure (*Table 28*). As we observed in Chapter 4, it was common practice to exclude from NSAIDs trials any patients who were liable to suffer renal compromise. Most of the trials could be described as 'equivalence' trials, comparing the new drug's effects with those of an existing agent, not making a comparison with an untreated state. Consequently, the trial reports did not yield any adverse renal events. Since the trials were small, they were probably underpowered even to function well as 'equivalence' trials with regard to safety. In the 'real world', clinical practice appears to have been less restrictive and the MEMO data show how the risk of adverse renal events was greater for men than for women, and that the risk increased with age and with length of period on NSAIDs for people of both sexes.

TABLE 28 *Cox-1 NSAIDs: acute renal failure (ARF) in trials and in MEMO cohort (rates are per 1000 patients in trials and per 1000 patient-years in MEMO cohort)*

	NSAIDs trials for OA patients on NSAIDs (mainly knee and/or hip OA)	NSAIDs trials for OA patients on placebo (mainly knee and/or hip OA)	Patients on NSAIDs in MEMO cohort (any diagnosis)
Rate of incident ARF	No events	No events	2.2
Excess risk of incident ARF in men compared with women	No events	No events	+79% (adjusted)
Excess risk of incident ARF in older people compared with younger people	No events	No events	+370% for people 70–79 years +779% for people 80+ years (adjusted and compared with people 50–59 years)
Excess risk of incident ARF with higher coverage/doses of NSAIDs	No events	No events	+38% for medium coverage[a] +69% for high coverage[b] (adjusted and compared with no current NSAID use)

[a] Medium coverage was defined as from 25% to <50% of days in the 1-year period being covered by an NSAID prescription.
[b] High coverage was defined as ≥50% of days in the 1-year period being covered by an NSAID prescription.

NSAIDs: discussion

The socio-demographic profile of NSAIDs trial samples was closer to the 'on treatment' and 'with potential need' populations than was the case with statins. Women tended to be represented proportionately in trials, although the average age of trial participants was probably slightly lower than that of analgesia users with OA. The trials did not reveal that socio-demographic factors such as sex and age were associated with gradients of risk of adverse events, as were increasing periods of exposure to NSAIDs. For example, a patient who was male, >60 years and taking NSAIDs for a prolonged period would build up an aggregated risk of a GI or renal adverse event as a result of all three of these factors. Our data suggest that the 'older, old' (late 70s and older) already bear a considerable risk of adverse events, which increases still further when the level of NSAIDs consumption is taken into account. This was not apparent from the trials.

We might speculate that risk of nephrotoxicity in an NSAID-medicated population has been underestimated by clinicians for two main reasons. First, the critical literature has tended to focus on adverse events in people with less than optimum renal functioning, a seemingly distinct high-risk group. Second, trialists have tended to remove from their samples anyone with any degree of renal risk, eliminating adverse renal events in the experimental situation, making it appear that NSAIDS carry little risk for the general population. Hence the critical studies and the trials seem to portray a dichotomous situation where there is a discreet group of renally vulnerable patients, who must be protected, whereas people outside this group do not have an appreciably raised risk. The issue might better be approached from a socio-demographic point of view, in particular from the perspective of age-related changes in physiological functioning. Since the distribution of renal functioning varies throughout the population and declines with age, there is a sense in which all older people have a degree of renal vulnerability.

NSAIDs: conclusions

There was no evident bias towards under-representation of women in trials of NSAIDs for OA. Women made up similar proportions of the 'on treatment' population, the 'with potential need' population and the trial samples. Older people, despite their level of potential need and use of analgesics, were probably slightly under-represented in NSAIDs trials. The particular vulnerability of the 'older, old' was not apparent

from the trials. It is unlikely that ethnic groups are represented in NSAIDs trials according to their needs. The lack of attention paid to socio-demographic characteristics in NSAIDs trials has meant that variation in adverse events by age and sex has not received due emphasis. Since, in addition, risk of toxicity varies with exposure to NSAIDs, the trials fail to show how some patients may build up an accumulation of risk factors.

Summary: disparity in NSAIDs samples and populations

- For NSAIDs for treatment of OA, we compared the socio-demographic profiles of trial samples, the 'with potential need' population and the 'on treatment with analgesia' population.
- Women were appropriately represented in NSAIDs trials.
- Women made up 69% of NSAIDs trial samples, of the 'with potential need' population and of the 'on treatment' population.
- Older people, aged ≥ 65 years, made up 59% of the 'on treatment' population, but these people were probably slightly underrepresented in trials.
- Levels of involvement in trials, need and treatment by ethnic group were not clear.
- Most NSAIDs trials did not report the ethnic profile of their samples.
- In cohort data, serious GI and renal adverse events were related to socio-demographic factors; men were at greater risk than women and risk increased with age in both sexes.
- The risk of renal events due to NSAIDs was not evident at all from our sample of trials, although GI side-effects were reported.
- The association of adverse events due to NSAIDs with socio-demographic factors has not been made clear in trials, but has become evident in 'real world' cohort data.

Chapter 11

Exploratory evidence synthesis of statins outcomes for women and older people

Background and objective

In the preceding chapters, we focused on ascertaining disparities between the representation of socio-demographic groups in trials and the socio-demographic characteristics of people who receive or need treatment in the clinical practice. We also explored how outcomes in trials might differ from outcomes in clinical practice, owing to trial samples being socio-demographically unrepresentative. For example, in Chapter 6 we reported how the incidence of adverse effects of NSAIDs in a community cohort varied strikingly according to age and sex, and also by dosage, co-medication and clinical history; such a pattern was not apparent from the trial reports. In Chapter 3, however, we concluded that the outcomes, in terms of relative risks, for women and older people within statins trials were similar to those for the majority of people in the trials. In this chapter, we set out in detail the reasoning and calculations behind this conclusion.

Indeed, the pathway of considerations leading to this conclusion has a further significance. It might be contended that the level of representation of a socio-demographic group (such as women) within a trial need not necessarily be so large that it produces a highly precise outcome statistic for that specific group. Even if outcomes for such a group do diverge from the overall 'average effect' observed in each trial, simple techniques such as meta-regression, meta-analysis and induction from other relevant research could, arguably, be applied to data from a number of trials to produce an evidence synthesis for such a group.

Having noted in Chapter 3 the relative under-representation of women, older people and ethnic minorities in our series of statins RCTs, we applied evidence-synthesis techniques to our set of secondary prevention trials to see if the latter provided an adequate evidence base in these groups (it was not possible to follow similar procedures with data from the sample of NSAIDs trials as the main therapeutic end-points, which were pain and movement outcomes, differed greatly between trials). To obtain a complete picture, we also reviewed serious adverse events in all available statins trials.

Our objectives were: to ascertain whether the statins trials, when taken together, provided a valid and adequate evidence base for the effectiveness of statins in these underrepresented groups; to estimate the level of relative effectiveness in these groups; to see whether these levels of effectiveness differed greatly from the outcomes in the well-represented groups; and to compare our findings in the set of trials with results from later, landmark statins trials to see if the latter corroborate the former.

Methods

We examined mortality, combined cardiovascular outcomes and serious adverse events for women and older people in our set of statins RCTs for secondary prevention. As very few secondary prevention results specific to socio-demographic groups were reported outside the four large RCTs published within our original search period (CARE,[113–118] 4S,[80–91] LIPID,[128–131] GISSI-P,[139,140] we concentrated on these trials. We were able to compare estimates from the earlier trials with results from the Heart Protection Study[184,185] and a study in older people, the PROSPER trial,[186,187] which have been published recently. Separate results for ethnic groups were not provided by any of the trials conducted in the developed world, so, with regard to ethnic minorities, we reluctantly abandoned our objectives at an early stage. We achieved the evidence synthesis by using the following techniques:

1. *Assessment of trial quality*. Following the recommendations of the Cochrane Handbook,[269] we assessed the quality of the four large secondary prevention trials in terms of concealment of the allocation sequence and double or assessor blinding. For concealment of allocation, we distinguished between adequately concealed trials (those that reported central randomisation, precoded drug packs administered serially, sequentially numbered,

sealed opaque assignment envelopes) and inadequately or unclearly concealed trials (those that reported an inadequate approach, such as alternation, open random number tables, or lacked a statement on concealment). For blinding we distinguished between trials that were described as double-blind or assessor-blind and those that were not. We noted whether or not the trials were conducted on an 'intention-to-treat' basis and how trialists dealt with the issue of how patients lost to follow-up might bias the results.[270] We also carried out a quality assessment for the Heart Protection Study and PROSPER.

2. *Review of secondary prevention trial outcomes*. We reviewed all-cause mortality or combined cardiovascular outcomes reported specifically for women and for men in the four large secondary prevention trials (usually RRs or risk reductions from Cox regression analyses). The constituent events of combined cardiovascular outcome varied slightly between trials.
3. *Meta-regression*. We extracted numbers of deaths (usually given for men and women combined) from all secondary prevention trials in our set to calculate a crude RR estimate (risk ratio) with SE, for each trial, as we had also done in Chapter 3. As we knew the proportion of women in each trial, we were able to perform random effects meta-regression (using the metareg command in STATA), to see whether there was any association across the trials between the proportion of women included and the outcome of mortality.
4. *Meta-analysis*. From the four large secondary prevention trials, we extracted the actual numbers of events for the combined cardiovascular outcome according to sex, and pooled them (using the metan command in STATA) in fixed-effects meta-analyses for women and for men separately. For the LIPID trial we derived event numbers from percentages of patients reported as suffering an event. (Note: we used this approach for simplicity and clarity, as subgroup data were reported as hazard ratios in some trials and as risk reductions in others.)
5. *Review of analogous trials*. We reviewed findings specific to women in the other trials in our series, which we had classified as primary prevention or mixed primary/secondary prevention. The findings of these analogous trials could be regarded as having implications for the use of statins in secondary prevention. In particular, we wished to discern whether there was a clear differential in effectiveness between men and women in the primary or mixed prevention trials. If there were any marked differentials in effectiveness, it would indicate the need for caution with regard to any evidence in the secondary prevention trials which showed similar levels of effect in both men and women, unless that evidence were very strong. In a similar fashion, we scrutinised data relating to serious adverse events in the analogous trials in order to detect any sex-related trends. If statins tended to produce serious adverse events more frequently in women than in men (or vice versa) in primary or mixed prevention trials, it was probable that secondary prevention patients would also be at risk. In other words, we were assuming that toxic effects would have an epidemiology across trial samples, which was not affected by the preventive aims of the trialists.
6. *Comparison with the later large trials*. We also examined findings from the later Heart Protection Study and PROSPER trial to see how the results of these trials, which had relatively high representation of women and older people, compared with the conclusions of our evidence synthesis.
7. *Second iteration*. We then repeated procedures 2–6, this time comparing results specific to older people with results specific to younger people.

Results

Results: quality of trials

All four large trials had largely favourable indicators of quality. All reported an adequate method of concealment of allocation (for LIPID confirmed in a personal communication). All were patient-blind and assessor-blind with the exception of GISSI-P, which became an 'open' trial when many control patients were given statins for ethical reasons. All four trials reported analysis on the intention-to-treat principle. LIPID and CARE were explicit concerning patients analysed and we judged them unlikely to have suffered from attrition bias. 4S and GISSI-P appeared to have included all patients in analysis, but could have been more explicit about this. The later trials, Heart Protection Study and PROSPER also had favourable indications of quality, in terms of adequate concealment of allocation and double-blinding; both trials presented flowcharts in their main reports and we judged it unlikely that they had suffered from attrition bias.

Overall results of trials

The findings shown in a cumulative meta-analysis plot (*Figure 16*) demonstrated that a strong and

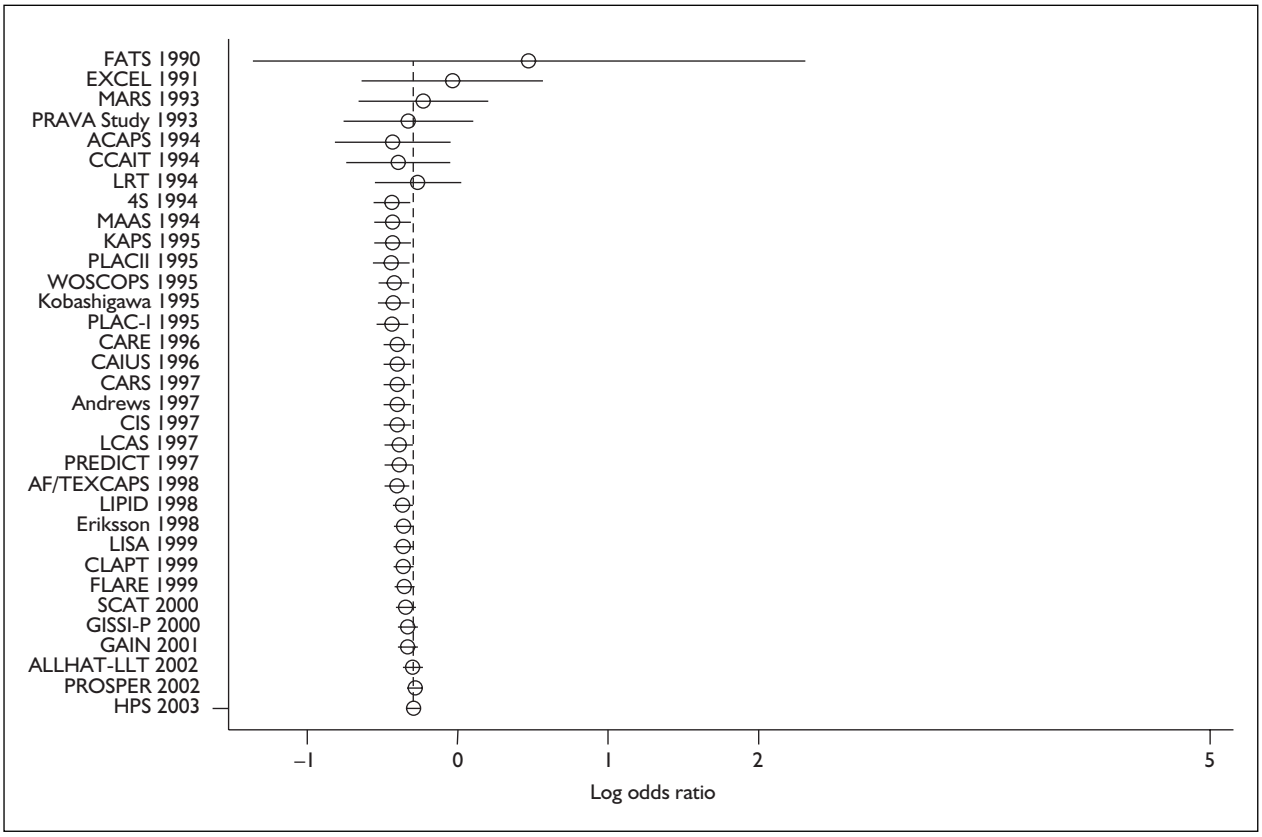


FIGURE 16 *Fixed-effects meta-analysis of all-cause mortality from statins trials of secondary prevention*

unequivocal benefit from statins treatment was apparent following publication of the 4S trial ($p < 0.0001$, Z-test = 6.8) in 1994. With the publication of the Heart Protection Study in 2003, the overall effect was beyond any doubt ($p < 0.0000001$, Z-test = 12.2) and effects for different patient groups were also estimated much more precisely.

Results for women: main outcomes in secondary prevention trials

The main results specific to women from the four large trials are presented in detail in *Table 29*. Overall, the results from the four large trials for the combined cardiovascular outcome did not present a definite picture of benefit for women. There was no evident risk reduction for women in LIPID or GISSI-P, although benefit was evident in CARE and 4S. Only 4S reported on mortality by sex and here there was no definite benefit for women.

Results for women: meta-regression

Meta-regression of the proportion of women in each trial against the trial effect size was conducted, but the limited nature of the data made further adjustment for confounding by age impossible and the results are not presented here. Individual patient data meta-analyses will be needed to examine whether effect sizes differ materially between men and women, although on the evidence examined this seems unlikely to be the case.

Results for women: meta-analysis

We performed meta-analyses using the numbers of events for the combined cardiovascular outcome. Forest plots are shown for women in *Figure 17* and for men in *Figure 18*. The combined estimate for women was 0.78 (95% CI 0.66 to 0.93), indicating that statins reduced the RR of cardiovascular events (mostly coronary death or non-fatal MI) by 22%. This magnitude of benefit in women remained robust when we removed the open trial GISSI-P from the meta-analysis. The combined estimate for men was only slightly more favourable, 0.75 (95% CI 0.70 to 0.81), and again, was robust if the open trial was removed from the meta-analysis. These meta-analyses indicate an approximately equivalent level of effectiveness for secondary prevention of the combined cardiovascular outcome in women and in men.

TABLE 29 *Mortality and combined cardiovascular outcomes for women and men reported in the four large RCTS of statins for secondary prevention (interaction results shown where reported)*

Trial	Mortality: point estimate (95% CI)	Description of combined cardiovascular outcome	Combined outcome result point estimate (95% CI)
4S 1994	No benefit for women RR in women was 1.16 (0.68 to 1.99), in men 0.65 (0.53 to 0.80)	CHD death or non-fatal MI or cardiac resuscitation	Similar levels of RR by gender: 0.66 (0.48 to 0.91) in women, 0.66 (0.58 to 0.76) in men
CARE 1996	Not reported	CHD death or non-fatal MI	Risk reduction was greater in women than men: 43% (4 to 66) in women and 21% (4 to 35) in men Interaction between sex and treatment, $p = 0.05$
LIPID 1998	Not reported	CHD death or non-fatal MI	No clear risk reduction in women: 11% (–18 to 33) in women, 26% (17 to 35) in men. But interaction was not evident
GISSI-P 2000	Not reported	Death or non-fatal MI or non-fatal stroke	Risk reduction not evident in women and weak finding in men: 1.08 (0.61 to 1.93) in women, 0.87 (0.66 to 1.14) in men

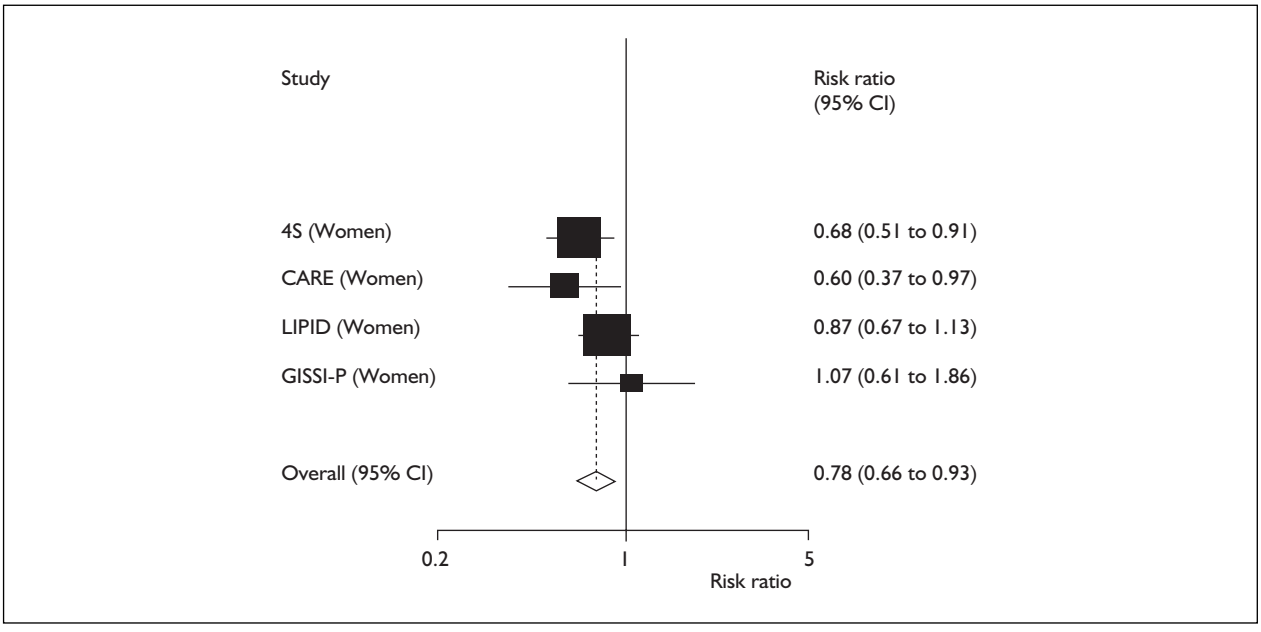


FIGURE 17 *Meta-analysis of combined cardiovascular outcome event data for women in four large trials of statins for secondary prevention. The heterogeneity χ^2 statistic was 3.84, with 3 degrees of freedom,* $p = 0.28$.

As a comparison of *Table 29* and *Figure 17* reveals, our recalculations of RRs (risk ratios) using event data from the trial reports were sufficiently close to the original RRs (hazard ratios) produced from Cox regression analysis models to make this a meaningful exercise.

Results for women: analogous trials

The trials AFCAPS/TEXCAPS, EXCEL, Pravastatin Multinational Study and Erikkson were not classified as secondary prevention but included women and contained at least 1000 patients. AFCAPS/TEXCAPS was a primary prevention trial

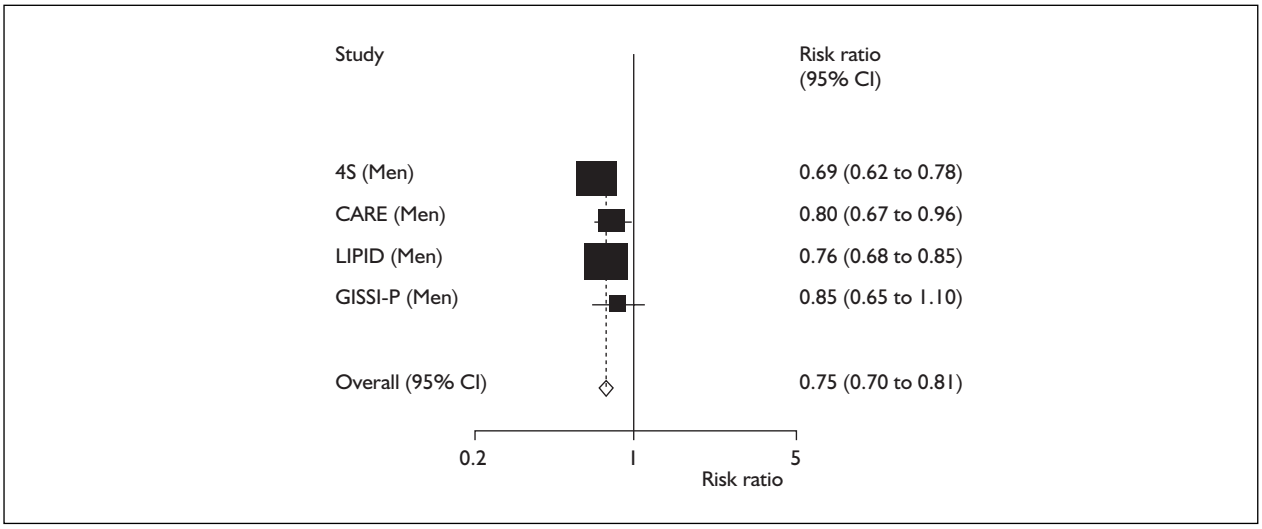


FIGURE 18 *Meta-analysis of combined cardiovascular outcome event data for men in four large trials of statins for secondary prevention. The heterogeneity χ^2 statistic was 3.08, with 3 degrees of freedom,* $p = 0.38$.

for patients with average total cholesterol levels, of whom 15.1% were women. The RR of the combined cardiovascular outcome (fatal or non-fatal MI, unstable angina, sudden cardiac death) was 0.63 (95% CI 0.50 to 0.79). Risk reduction was greater (46%) in women than in men (37%), but the event rate in women was low (20 events in 997 women over 5.2 years). This trial cannot, therefore, be regarded as providing strong evidence about the effects of statins on cardiovascular events in women, which could be used in our evidence synthesis. The other three trials were classified as mixed prevention trials. However, in none of these trials were separate data reported for women. WOSCOPS, a major trial in the mixed prevention group, was of course conducted exclusively in men.

Results for women: Heart Protection Study

The later, large Heart Protection Study confirmed the effectiveness of statins for reduction of cardiovascular events in 15,454 men and 5082 women. Subgroup results were presented for a broad category of major vascular events (subsuming the primary end-point, combined cardiovascular outcome of CHD death or non-fatal MI). The proportions of women in the trial suffering the combined cardiovascular outcome were reported as 14.4% in the statins arm and 17.7% in the placebo arm. For men the respective proportions were 21.6 and 27.6%. In approximate terms, these represent RR reductions of about 22% for men and 20% for women, reductions of a similar magnitude to those we estimated in our meta-analyses. (It should be noted that as an average of 17% per annum of the control group were taking non-study statins, the trialists projected that the true benefit of statins in terms of risk reduction in men and women might be around a magnitude of 30%.)

Results for women: severe adverse events

As we have noted in Chapter 3, severe adverse events were rare in our set of trials of statins. The only case of rhabdomyolysis, which is a life-threatening condition, in a secondary prevention trial was in a 60-year-old woman on simvastatin in 4S. However, we could not rule out the possibility that statins would produce more cases of rhabdomyolysis, when prescribed in large populations of patients. In the very large Heart Protection Study there were five cases of rhabdomyolysis in the simvastatin arm and three cases in the control arm (0.05 versus 0.03%), which does not provide sufficient evidence to reject the null hypothesis of no excess risk. As we have said in Chapter 3, breast cancer cases did occur in the secondary prevention trials, but if one takes all four large trials into account, there is no evidence of an overall excess of breast or other cancers in women due to statins.

Nevertheless, as *Table 29* shows, mortality data, as distinct from combined cardiovascular outcomes, were not well reported for women, even though a mortality statistic is a simple way of summarising the balance of benefit or harm resulting from an experimental treatment for a life-threatening disease. Given the marked mortality benefits demonstrated overall in these trials, the clear

TABLE 30 *Mortality and combined cardiovascular outcomes for older and younger people reported in the four large RCTS of statins for secondary prevention (Interaction results shown where reported)*

Trial	Younger and older age-groups (in years) compared	Mortality: point estimate[a] (95% CI)	Description of combined cardiovascular outcome	Combined outcome result point estimate[a] (95% CI)
4S 1994	35–59	0.63 (0.45 to 0.88)	CHD death or non-fatal MI or cardiac resuscitation	0.61 (0.51 to 0.73)
	60–70	0.73 (0.58 to 0.92)		0.71 (0.60 to 0.86)
CARE 1996	<65	Not reported	CHD death or non-fatal MI	13% (–8 to 31)
	65–75			39% (18 to 55) (risk reductions)
				$p = 0.06$ for age group and treatment interaction
LIPID[b] 1998	31–55	0.76 (0.64 to 0.91)	CHD death or non-fatal MI	32% (12 to 48)
	55–64			20% (3 to 34)
	65–69	0.79 (0.68 to 0.93)		28% (11 to 41)
	70–75			15% (–8 to 33) (risk reductions)
				No evidence of age group and treatment interaction, $p \geq 0.08$
GISSI-P 2000	<65	Not reported	Death or non-fatal MI or non-fatal stroke	0.71 (0.49 to 1.03)
	≥65			1.11 (0.80 to 1.55)

[a] Relative risks (from Cox regression analysis) unless stated otherwise.
[b] LIPID cardiovascular outcomes are by four age groups, but mortality is reported by two groups.

cardiovascular benefits for women, the suggestive evidence of the meta-regression, and the overall absence of excess of cancer cases in either sex, it is most improbable, however, that there would be an excess of overall mortality for women due to statins.

Summary: evidence synthesis for women

- As results for women were not well reported in our set of statins RCTs, we produced a synthesis of available evidence for secondary prevention from the set.
- The evidence consisted of the sex-specific results reported in major trials, meta-regression (of RR of mortality on percentage of women), a meta-analysis of combined cardiovascular events and a consideration of serious adverse event data from relevant trials.
- The evidence synthesis in this set of trials strongly supported the effectiveness of statins to reduce the risk of death and cardiovascular events to the same degree in women as in men.
- Analogous trials contributed little useful data in this context.
- Insufficient data were available to make inferences about the possibility of an increased risk of rhabdomyolysis in statins users, or whether this risk was elevated for women.
- The later Heart Protection Study, with its large sample size, has confirmed the effectiveness of statins in both men and women.
- The latter study also contains further evidence that rhabdomyolysis might be associated with simvastatin use, although the event rate was low.

Results for older people: main outcomes in secondary prevention trials

Results specific to older people from the four large trials are presented in detail in *Table 30*.

Overall, the results given in the trial reports for the combined cardiovascular outcomes indicated benefit from statins for older people up to the age of about 75 years, although GISSI-P, an open trial with a low event rate, was exceptional in showing

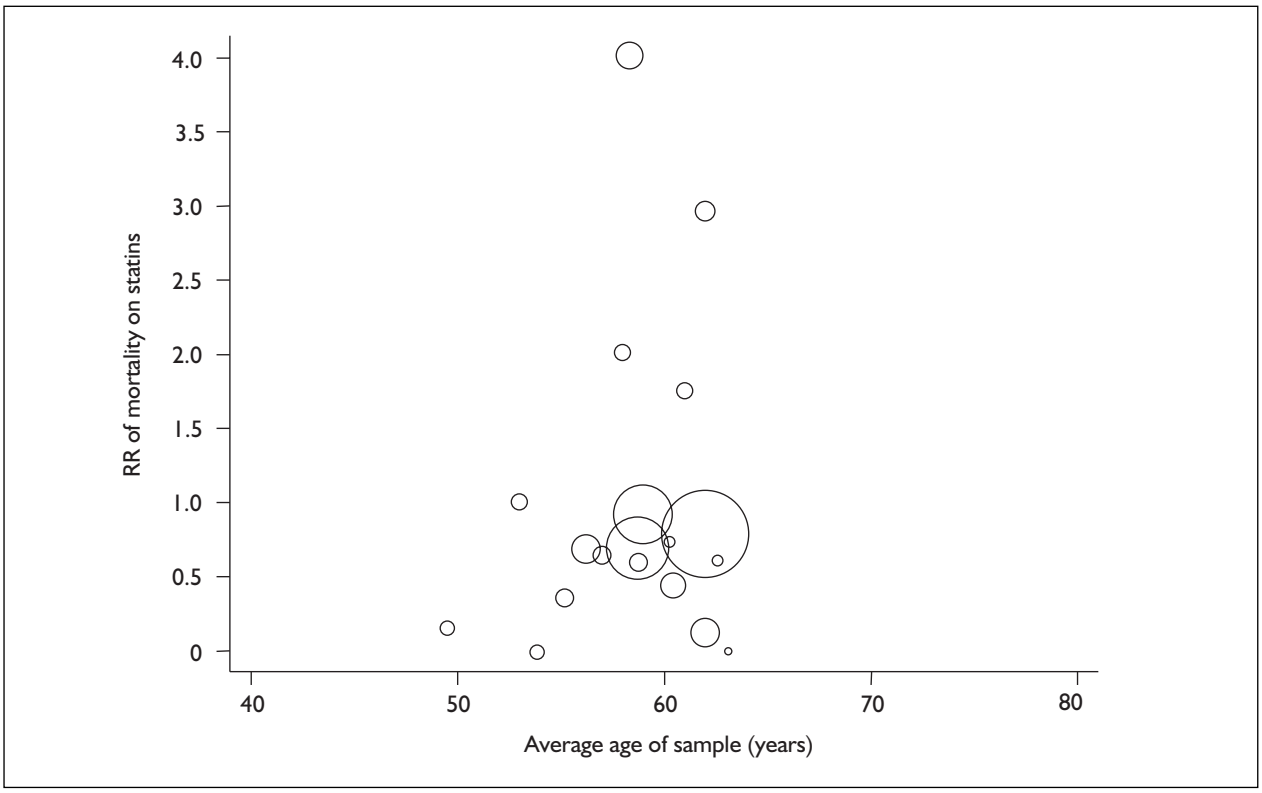


FIGURE 19 *RR of mortality in statins arm plotted against average (usually mean) age of trial sample in statins RCTs for secondary prevention. The circles are in proportion to sample size of trial; decreasing y values denote decreasing RR of mortality on statins.*

no obvious gain for older people. However, the data from these trials are suggestive of a decrease with age of risk reduction, although differences between point estimates for older and younger people do not reach conventional levels of statistical significance in any of the trials.

4S and LIPID also reported on all-cause mortality for older and younger people. Here the pattern was similar to that observed in the cardiovascular outcomes, that is, indicating clear benefit in older people but being suggestive that, in comparison with younger people, this benefit might be of a smaller magnitude in terms of RR reduction. However, as the LIPID authors point out, because an older individual is at greater risk of cardiovascular events, the absolute risk reduction this person would receive from statins would exceed that gained by a younger person. A treatment may provide the same RR reductions in both a low-risk and a high-risk group, but it will prevent more events (per people treated) in the second group than in the first group.

Results for older people: meta-regression

The meta-regression did not suggest any relationship between the average age of samples and the mortality outcome. The meta-regression beta was 0.01 (95% CI –0.04 to 0.06). A plot of RR of mortality and average age of patients is shown in *Figure 19*.

Results for older people: meta-analyses

Forest plots for the meta-analyses of combined cardiovascular event data are shown in *Figures 20* (people aged ≥65 years) and *Figure 21* (people aged <65 years). With age 65 years used as the point of division, the combined estimates of RR were of a similar magnitude in younger and older people. The combined estimate was only slightly larger, that is, less beneficial, for older people (0.77 compared with 0.75) and the difference was below the conventional level of statistical significance. This similarity remained when GISSI-P, the open trial, was removed from both meta-analyses. An individual patient data (IPD) meta-analysis would be needed to confirm whether there was some degree of attenuation of the effectiveness of statins with increasing age up to 75 years, as suggested by *Table 30*.

Data for older people did not include anyone aged over 75 years except in the GISSI-P trial, which contributed the least statistical weight to the meta-analysis and was inconclusive in its findings

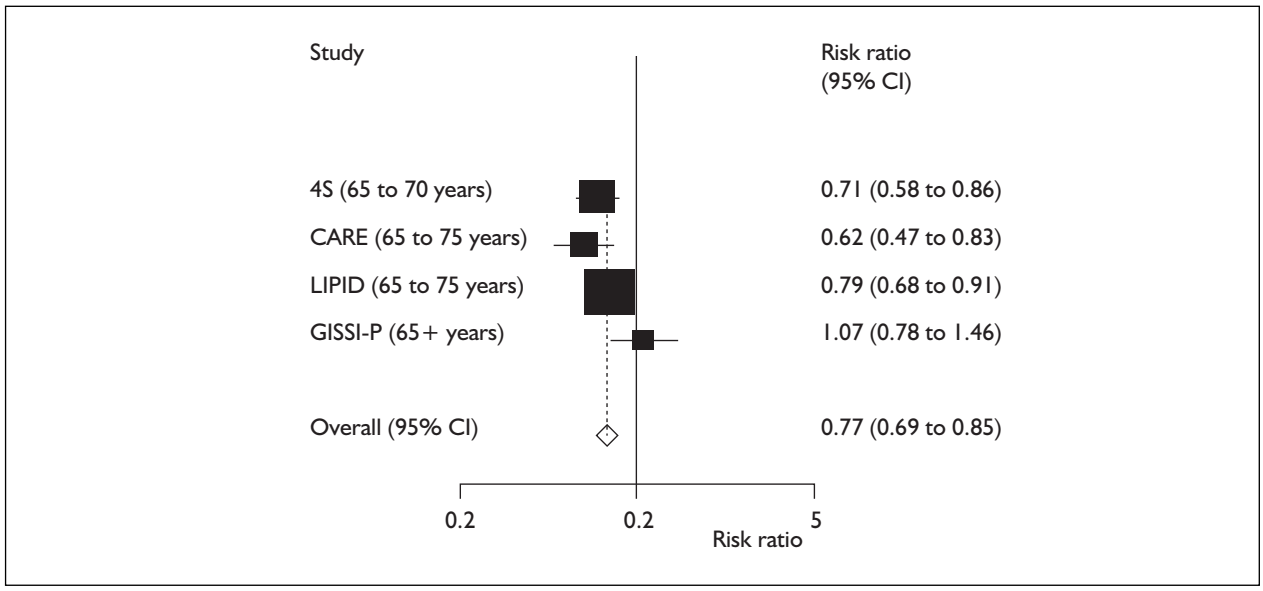


FIGURE 20 *Meta-analysis of combined cardiovascular outcome event data for people aged 65+ years in four large trials of statins for secondary prevention. Heterogeneity χ^2 statistic was 7.27, with 3 degrees of freedom,* $p = 0.06$.

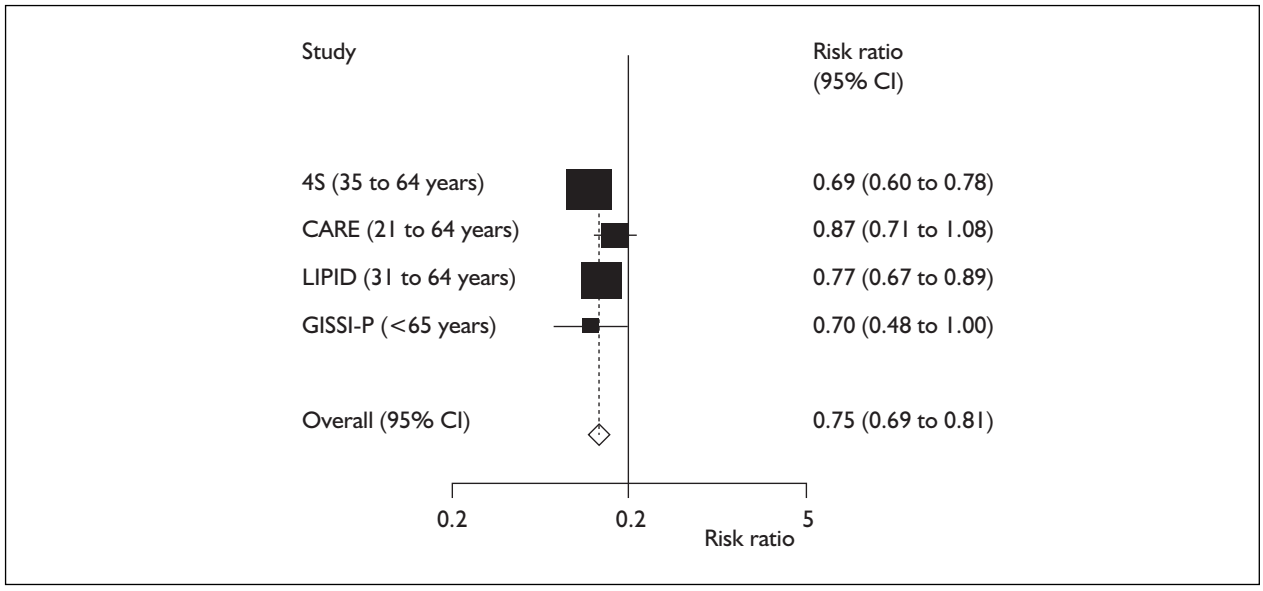


FIGURE 21 *Meta-analysis of combined cardiovascular outcome event data for people aged <65 years in four large trials of statins for secondary prevention. Heterogeneity χ^2 statistic was 4.06, with 3 degrees of freedom,* $p = 0.255$.

for older people. Thus, the meta-analyses did not give any information on the effectiveness of statins in people aged >75 years, who might be termed the 'older, old'.

Results for older people: analogous trials

The primary prevention trial AFCAPS/TEXCAPS reported on outcomes above and below the median age according to sex (57 years for men and 62 years for women). For the combined cardiovascular outcome, statins treatment was beneficial in both the older and younger groups, at a similar level to that observed in the sample as a whole. Effectiveness did not reach the conventional level of statistical significance in the older group, however. The mixed prevention trial WOSCOPS contained only men, but reported the combined cardiovascular outcome for men <55 years old and men aged ≥55 years; the respective risk reductions were 40 and 27%, but they were not different in terms of statistical significance.

Results for older people: Heart Protection Study

The Heart Protection Study, with an age range of 40–80 years, confirmed the effectiveness of statins for reduction of cardiovascular outcomes in younger and older patients. The trialists reported data for major vascular outcome (a broader category than the combined cardiovascular outcome) for numerous subgroups, including age subgroups. In the under-65s, the proportions having a major vascular outcome were reported as 16.9% in the statins arm and 22.1% in the placebo arm. For people aged 65–69 years the respective proportions were 20.9 and 27.2%. For the oldest group, 70–80 years, the respective proportions were 23.6 and 28.7%. In approximate terms these represent RR reductions of about 24% (under-65s), 23% (65–69 years) and 18% (70–80 years). There is again a suggestion here that older people gained less benefit in relative terms. It should be noted, though, that these outcomes did not differ from one another at the conventional level of statistical significance and no statistical interaction between age and statins treatment was detected (trend χ^2 statistic = 0.73).

Results for older people: PROSPER

The PROSPER trial is a landmark study in the effectiveness of statins in older people, as it was conducted solely in the age range 70–82 years and so presents extensive data on beneficial and adverse outcomes specific to older people. PROSPER confirmed that statins reduce the rate of cardiovascular events in older people, including people aged >75 years. Although, strictly speaking, PROSPER was a mixed prevention trial, because it included a large proportion of the 'older, old', it must be given serious consideration in its implications for secondary prevention. In line with suggestive evidence from other trials such as the Heart Protection Study, the RR reduction (15%, 95% CI 3 to 26%) for these comparatively old people was smaller than those in trials that mainly involved people aged ≤75 years (which we had estimated in meta-analyses at about 25%). However, as we have remarked previously, because an older individual is at greater risk of cardiovascular events, the absolute risk reduction this person could, in theory, receive from statins would exceed that gained by a younger person. No benefit in terms of mortality was observed in PROSPER, but the trial was not powered for this purpose.

Results for older people: severe adverse events

The issue of rhabdomyolysis has been addressed above (in section 'Results for women: severe adverse events', p. 77). It is conceivable that this adverse effect due to statins might occur more frequently in older than younger people, but the relatively small proportions of older people in the trials might have obscured this. Furthermore, as we have noted, older people in statins trials tended to be ≤75 years old. LIPID was unusual in reporting on adverse events amongst older people (65–75 years); there was a higher risk of incident cancer in older people on pravastatin treatment, the RR being 1.14 (95% CI 0.98 to 1.32, test for treatment-age interaction $p = 0.012$). Data suitable for comparative purposes were not reported in other trials, thus indicating the data-dependent nature of this finding and making this most likely a Type 1 error. All-cause mortality was reported only in two of these four large trials, but indicated clear benefit from statins.

Results for older people: the 'older, old' in the Heart Protection Study and PROSPER

Our set of statins trials had collectively provided strong evidence of the beneficial effects of statins in people up to the age of about 75 years and this was confirmed in the two large later trials, although adverse effects were not so well covered. In contrast, the set presented few data on how statins might benefit or adversely affect people older than 75 years, the 'older, old', a group of people who are more likely to have various combinations of impairment, co-morbidity, co-medication and psycho-social problems. Indeed, people in this age group were usually excluded from statins trials. For evidence relating to the 'older, old' we relied on the two later trials, the Heart Protection Study and PROSPER. These trials have come late in the experimental history of statins, over a decade after the first trial in our set, but have now contributed substantial numbers of older people to the evidence-base, respectively 5806 and 5804 people aged ≥70 years. The exact number of those who were aged ≥75 years was not reported, but was probably less than half the figure for all people in their 70s. The total number of patients in the four large trials in our set plus the Heart Protection Study and PROSPER was 48,228, so from one perspective over-75s have come to form about one-tenth of the evidence base but only at a late stage.

Our prime sources for the 'older, old', the Heart Protection Study and PROSPER, identified people aged 70–80 and 70–82 years, respectively, as their oldest groups. Therefore, we used data from these age bands and assumed that since the 75-year

TABLE 31 *Changes in absolute rates of events associated with statins treatment in PROSPER: rates are shown as events per 1000 patients (95% CI) (cancer excludes non-melanoma skin cancer)*

	Combined cardiovascular outcome	Rhabdomyolysis cases	Incident cancer	Balance of benefits and harms[a]
PROSPER 70–82 years (n = 5804)	Reduction = 21.2 (2.8 to 39.7)	No events	Increase = 16.4 (2.8 to 30.1)	Reduction = 4.8 (–16.8 to 26.4)

[a] This was the balance of changes in the event rates per 1000 people of combined cardiovascular outcome versus incident cancer, i.e. a measure of net health gain.

mark has no special biological or medical significance (despite its attraction for epidemiologists and demographers), these data would be a reasonable guide to how the 'older, old', people ≥75 years old, had fared with statins.

We considered the following pessimistic hypothesis: if effectiveness attenuated with age, there might be a point in later old age (when people are more sensitive to the adverse effects of drugs) at which the benefits of statins might be almost counterbalanced by their adverse effects. We therefore wished, using the most appropriate data reported by the trialists, to move beyond RRs to absolute risks.[271] We wanted to compare the reduction in absolute rate of cardiovascular events (benefit attributable to statins) with the increase in absolute rates of rhabdomyolysis and of incident cancer (assuming that these adverse effects were actually caused by statins). The increases in adverse event rates in the Heart Protection Study were so remarkably small in the sample as a whole, and none were statistically significant, that older people, in all likelihood, gained net overall benefit from statins treatment. PROSPER reported the data we required for our age group of interest (*Table 31*). Owing to an excess of cancer in the pravastatin arm, the net benefit for statins users (comparing the combined cardiovascular outcome rate reduction with the cancer rate increase) was a reduction in undesirable events of 4.8 per 1000 people; this can be expressed as a number-needed-to-treat (NTT) (for benefit) of 208.

The PROSPER trialists noted the excess of incident cancer in the pravastatin arm (25% more cases than in the placebo arm). Their *post hoc* meta-analysis of four pravastatin trials (people of all ages included) indicated only a slight excess of cancer cases associated with pravastatin, and this finding did not reach the 5% significance level (RR 1.06, 95% CI 0.96 to 1.17). Their *post hoc* meta-analysis of cancer cases in trials testing a statin other than pravastatin did not show any excess associated with statin treatment. Consequently, the PROSPER trialists interpreted the cancer outcome in their trial as a chance finding (a Type 1 error) or as due to a selection bias in the trial.

Results for older people: observations on the 'older, old'

For the purpose of our own methodological enquiry, we made a number of observations at this stage. Our original set of trials had not been helpful in informing us about the effectiveness of statins in people aged >75 years. For this we had utilised the two landmark trials that came late in the history of statins. These confirmed that statins were effective for cardiovascular secondary prevention in the 'older, old'. While RCT evidence has demonstrated only very low levels of serious adverse events and no excess in those treated with statins, it only became necessary to consider the issue of the balance of benefit and harm for the 'older, old' with publication of PROSPER. Statins were effective in PROSPER, but delivered a smaller RR reduction than in trials of younger people and an excess of cancers was found in those treated with statins. Our analysis demonstrates that even if these cancers were causally related to statins treatment (which seems unlikely), there is a net benefit from statins treatment at older ages.

It is conceivable that similar situations might arise on other occasions when researchers are investigating treatments in older people, particularly the 'older, old'. If we hypothesise treatments which are less potent in their therapeutic effects than statins, and which may have an attenuation of effect with age together with a more hazardous profile, the problem of discerning the benefit–harm balance could, in theory, be even more difficult to resolve without well-powered clinical trials devoted to this age group. In many areas of medicine there is no comparable large trials culture such as exists for

CHD, and consequently such problems may be more marked.

This same line of argument could also be extended to lower risk groups (i.e. groups at comparatively low risk of the main outcome of interest) if they are underrepresented in trials. If we hypothesise treatments which are less potent in their therapeutic effects than statins, for under-represented lower risk groups, which will have low event rates, we might find it difficult to estimate absolute rate reductions (with acceptable precision) and hence the cost-effectiveness of such treatments. We expand further the complementary nature of measures of relative and absolute effectiveness in Chapter 12.

Summary: evidence synthesis for older people

- We produced a synthesis of available evidence from this set of statins RCTs.
- This consisted of results specific to age groups reported in major trials, meta-regression (RR of mortality on average age), a meta-analysis of combined cardiovascular events and a consideration of serious adverse event data from relevant trials.
- The evidence synthesis strongly supported the effectiveness of statins for reducing the risk of death and cardiovascular events in older people aged ≤75 years.
- Trials in our set did not directly investigate the benefits of statins in the 'older, old' (75+ years).
- The later Heart Protection Study and PROSPER trial confirmed the findings from the earlier trials.
- PROSPER indicated the effectiveness of statins for people aged 70–82 years, but reported a smaller cardiovascular RR reduction than that observed in trials of younger people.
- As this age group is a higher risk group, absolute benefits for an individual would be greater than for a younger person.
- There are sound theoretical reasons to assess thoroughly benefits and harms of treatment in the 'older, old'.
- Such a benefit–harm assessment was rare in statins trials.

Methodological discussion

Meta-regression

Our meta-regression findings of mortality outcomes on percentage of women and on average age across the statins trials were conducted for illustrative purposes, demonstrating the limitations of meta-analysis based on published, rather than individual patient, data. The weaknesses of the methods have been described and discussed by Thompson and Higgins.[272] Meta-regression analyses observational relationships within trials, so it is a distinct possibility that confounding may occur in this type of analysis. The technique is liable to problems caused by low statistical power, usually a consequence of a relatively small number of trials and a limited range of values. Some authors (e.g. Higgins and colleagues[273]) have recommended using meta-regression solely to investigate differences that might be associated with trial characteristics rather than with patient characteristics and then only in a large set of trials. In this report, we consider the meta-regression findings to be essentially non-contributory and would not recommend their use in attempts to study subgroup effects.

Meta-analysis

Meta-analysis is a useful, well-established method of pooling results from trials, a technique that takes account statistically, through assigning weights, of the frequency of events and number of participants within each trial. The technique itself does not take into account the quality of the trials. The meta-researchers themselves must adopt strategies to allow for potential bias emanating from trials of lower quality.[269] Meta-analysis proved particularly useful to us in confirming the effectiveness in statins in women. We have also cited results from later trials to confirm that our meta-analytic findings from the four large trials were valid.

As we utilised subgroup data from trials, it is worth reiterating that some authors, such as Brookes and colleagues,[274] have argued that analysis of subgroups should be performed sparingly by trialists and that interaction tests for heterogeneity should support any findings.[274] When a number of subgroups and outcome measures are investigated, it is likely that, by chance, treatment efficacy will appear to be larger in some subgroups than in others.[275] Some early trials (e.g. LIPID, GISSI-P) reported a plethora of subgroup results, which run the risk of producing both Type I and II errors if formal interaction tests are not conducted. It is essential to bear in mind that virtually all trials, even those of the size of the large statins trials examined here, are only powered to examine main effects in intervention and control groups and lack statistical power for examination of subgroup effects. Therefore, interpretation of subgroup findings must always be guarded and should

consider whether the findings are consistent with the main effects observed.

Individual patient data meta-analysis

IPD meta-analysis, based on results from individual trial participants rather than aggregated results, would have been an appropriate way of confirming whether the effectiveness of statins did indeed diminish with age.[276] Meta-analysis of broad age-group results did not clarify the situation, although findings from the two later large trials to some degree supported the hypothesis of attenuation with age. An IPD meta-analysis would have allowed the relationship to be investigated in an even more rigorous manner, allowing us to obviate the problem of the different definitions used for age bands in trial reports. The IPD approach might also be particularly useful for investigation of those adverse events that might be related to a patient characteristic such as co-medication or co-morbidity. The Cholesterol Treatment Trialists (CTT) Collaboration is coordinating international IPD meta-analyses from cholesterol-lowering trials. A number of cycles have been planned according to a prespecified protocol.[276,277] A smaller pooling project has already published results.[278] For the reasons we have outlined, IPD meta-analysis is often considered to be 'the technique of choice' in evidence synthesis. The cost and time taken to establish IPD meta-analyses are a substantial barrier to their widespread use. However, as has been demonstrated by the Antithrombotic Trialists Collaboration, it is only with compelling evidence of benefit – to all categories of patient – that clinical practice can be moved forward.[279]

Analogous trials

Analogous trials did not prove very useful to us, mainly because reporting by specific socio-demographic group was even less common in the primary and mixed prevention trials than in the secondary prevention trials. However, this approach is worth considering for treatment-related adverse events, as the primary or secondary prevention status of patients is not likely to influence the level of toxic effects produced by a drug.

Severe adverse events

Clinical trials have to be very large if the rate of severe adverse events associated with a treatment is to be estimated accurately. This problem is therefore multiplied for adverse events that might have a higher incidence in particular socio-demographic groups. The four large statins trials reported reasonably well on some conditions such as female cancers, but we were not confident that these trials provided an adequately robust picture of serious adverse events in older people. As the 'older, old' were largely excluded we had no information at all on adverse reactions in this vulnerable group. Only the later Heart Protection Study and PROSPER were large and inclusive enough to have the potential to provide useful data in this respect. Of these two, only PROSPER presented sufficient data on adverse events for this group to allow a thorough benefit–harm comparison to take place. In this trial, the benefits of statins outweighed the apparent harms by a modest degree in the 'older, old'. The evaluation of benefit and harm in PROSPER was complicated by a possible Type 1 error in the cancer data. It is conceivable that for treatments that have a level of effectiveness lower than that of statins, the comparison of benefits and harms in the 'older, old' may be an even more difficult task. A fundamental issue is the ability to pin down whether a drug is or is not the cause of an observed excess of adverse events in a clinical trial. Collateral research giving a biological rationale for such harms may help.

Methodological conclusions

Meta-analysis is a useful way of making inferences from a number of trials about the effects of treatment in large, well-demarcated socio-demographic groups. IPD meta-analysis would be required for dealing with more subtle relationships, such as the attenuation of the effectiveness of a drug with age. In the exemplar drug we studied, statins for secondary prevention, meta-analysis allowed us to estimate the relative effectiveness of statins in two underrepresented groups, women and older people. The level of representation of women and older people (65–75 years) did not seem to affect to any appreciable degree the generalisability of the main trial outcomes.

On the other hand, these techniques would be of little use in investigating severe adverse events in any socio-demographic group until the amount of data available was very large indeed. The 'older, old' (≥75 years) were very poorly represented until late in the experimental history of statins. Conventional (i.e. derived from published data only) evidence-synthesis techniques would not have aided the investigator. Very few data for ethnic groups were provided by trials for analysis or meta-analysis and no conclusions about the generalisability of trial results to ethnic groups can be drawn. Likewise, for groups at comparatively low risk of disease events, problems might be

encountered in robustly estimating absolute rate reductions and projecting cost-effectiveness. The most straightforward solution would be for appropriate representation in clinical trials of socio-demographic groups and for the 'older, old' and ethnic groups in particular.

Summary: evidence-synthesis methodology

- We used evidence-synthesis techniques to see if our set of secondary prevention statins trials provided an adequate evidence base for women, older people and ethnic minorities.
- Data for ethnic groups were so sparse that we could not pursue our investigation in this direction.
- Meta-regression is commonly used in evidence synthesis, but is not ideal for investigation according to patient characteristics.
- Meta-analysis can be useful and valid in combining results from trials for socio-demographic groups, but considerations of trial quality must also be made.
- IPD meta-analyses are expensive in terms of time and money but can be used for robust ascertainment of subtle relationships, e.g. variation of effectiveness of a treatment with age.
- Analogous trials may have some value (such as for adverse events), but they often suffer from the same weaknesses as the main trials under scrutiny.
- For our exemplar drug, statins, the level of representation of women and older people (65–75 years) did not seem to affect greatly the generalisability of the main trial outcomes.
- The 'older, old' (≥75 years) were poorly represented in all but the most recent trials.
- Careful assessment of benefit and harm in this vulnerable group was seldom undertaken.
- If severe adverse events are likely to be associated with socio-demographic characteristics, such as age, large and inclusive trials would probably be necessary to detect them at an early stage.

Chapter 12

Epidemiological and statistical assumptions about trial exclusions: theoretical models of outcome, sample size and power

Background

In the previous chapter, we demonstrated how a highly effective and safe treatment, namely statins, produced similar levels of RR reduction in men and in women and in people of different ages (although the reduction was not so great in people aged >75 years). Hence, our results could be used to support the argument that there may be types of treatment where the 'average effect' of a trial is generalisable to people of both sexes and of all ages and where inclusion levels are not a significant influence on external validity. A similar situation seems to prevail for drug treatments for other common cardiovascular conditions such as hypertension[280] and atrial fibrillation.[281] However, a strong case can be made that the absolute effectiveness or harmfulness of a treatment is more pertinent than its relative effectiveness or harmfulness for decisions about treatment of individuals, resource allocation and trial design.

Measures of absolute and relative effect are, of course, complementary. Measures of relative effect tend to be more or less consistent across different groups of patients, and, if this is the case, provide a more 'portable' and readily communicated estimate of the effects of treatment. For example, it is easy to remember that statins treatment reduces the risk of vascular events by about 25%. However, absolute measures of effect differ for patient groups at different intrinsic levels of risk of vascular events. Consequently, absolute treatment effects and their reciprocals, NNT for benefit, differ between groups such as men and women, old and young. They are clearly essential in guiding clinicians and policy makers in the amount of work that has to be conducted in achieving health gain, and are central to cost-effectiveness calculations.

Measurement of absolute effect can be used to calculate NNT for one person to benefit and for one person to be harmed. This allows a clear evaluation of the balance of benefit and harm from a treatment and facilitates a calculation of cost-effectiveness. In other words, absolute risk differences may have more practical import than do RR differences. In this chapter we explore (in the context of consistent RRs such as those for statins) the effects of exclusions from trials on absolute effectiveness, cost-effectiveness, trial power and sample size requirements.

Objectives

We aimed to explore in statistical models and to demonstrate graphically how absolute effects (and so NNTs and cost-effectiveness ratios) of a hypothetical intervention would vary within trial samples according to the risk levels of trial participants in the 'untreated' state. We also explored how the power of trials and the sample sizes required in trials would vary according to 'untreated' risk levels.

Methods

We created the models using statistical functions and graphics in the Excel spreadsheet package. We adopted the risk of events in the control arm of the trials as a proxy for the 'untreated' risk levels and expressed this as the x variable in each model. (See section 'Note on control group rates', p. 88. The risk level in the 'untreated' state is also sometimes referred to as the 'baseline risk' or the 'underlying risk'.) This variable was continuous for modelling purposes, although in our interpretation we refer to 'high-risk' and 'low-risk' groups. In each model the curves are plotted for different possible values of RR reduction, expressed here as relative effectiveness (1 – RR). We have assumed that each value of relative effectiveness plotted would be consistent across all the groups with their different risk levels in the 'untreated' state. Cost-effectiveness ratios are the expenditure on treatment required to prevent one undesirable event, assuming for modelling purposes a cost of treatment of £100 per patient.

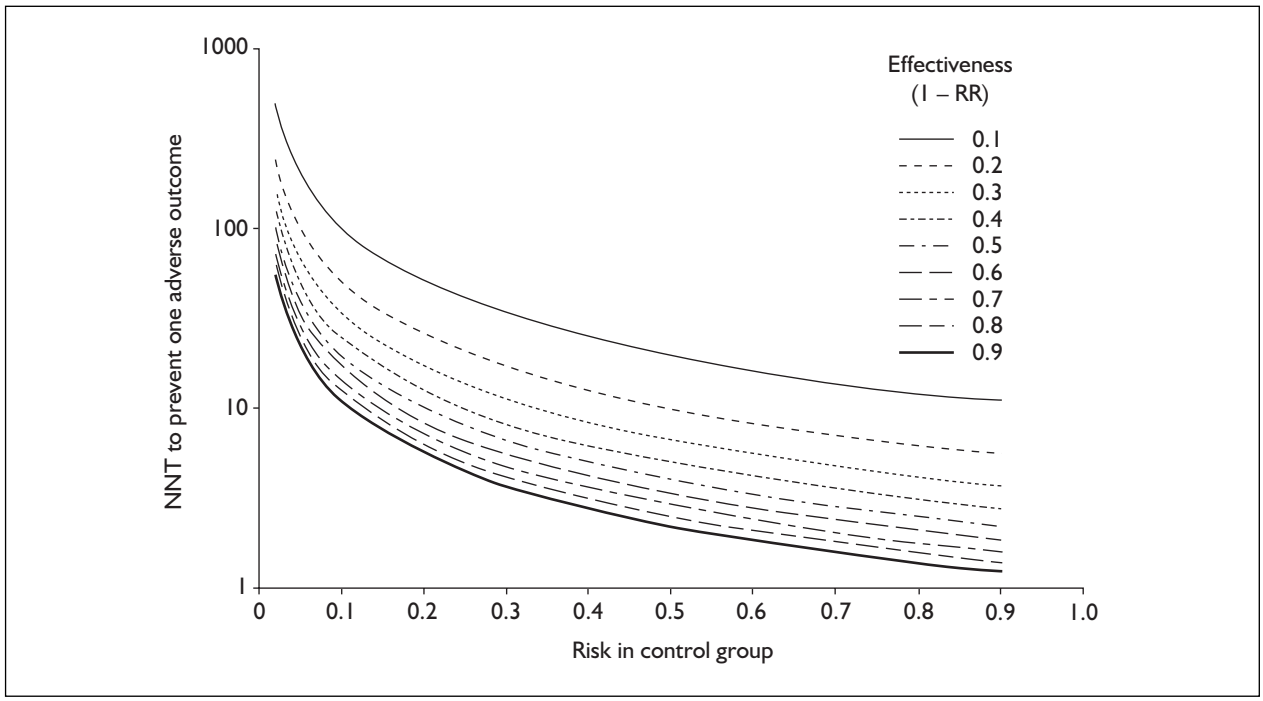


FIGURE 22 *NNT to prevent one disease outcome*

Note on control group rates

We have followed the conventional practice of adopting control group rates from trials (hypothetical trials in the present exercise) as a guide to the underlying risk of disease events in a population. It is, of course, possible in actual trials that selection bias will lead to the most impaired or vulnerable people being excluded from trials and so to a lower underlying risk of disease appearing in the trial than exists in the 'real world'. From a statistical perspective, if the RR reduction remained constant across all underlying disease risks, this type of selection bias would mean that the estimate of absolute effect would be too pessimistic. From a practical perspective, it is possible that very vulnerable people would not, in the event, achieve the same RR reductions as people who were admitted to the trial.

Results

Epidemiological assumptions

Figure 22 demonstrates that at a given control group (or underlying) level of risk, the more effective treatments have a smaller NNT, and that at a given level of treatment effectiveness NNT decreases as control group risk increases. If the relative effectiveness of the intervention remains the same at all risk levels (that is, at all prevalences of the disease outcome one aims to prevent) then:

- The absolute effect (risk difference, or proportion of treated people who would benefit from treatment) will be underestimated by exclusion of high-risk populations, and will be overestimated by exclusion of low-risk populations (*Figure 22*).
- Therefore, cost-effectiveness will be overestimated by exclusion of low-risk populations (i.e. will be overoptimistic) and will be underestimated by exclusion of high-risk populations (*Figure 23*).

The same applies to risks of adverse events, the unwanted side-effects of treatment. If the relative riskiness of the intervention (its tendency to produce side-effects) remains the same at all risk levels of side effects in the 'untreated' state, then:

- The absolute effect (risk difference, or proportion of treated people who will suffer side-effects as a consequence of treatment) will be underestimated by exclusion of high-risk populations, and will be overestimated by exclusion of low-risk populations.
- If side-effects increase costs or reduce net benefits, cost-effectiveness will be underestimated by exclusion of low-risk populations (i.e. will be overpessimistic) and will be overestimated by exclusion of high-risk populations.

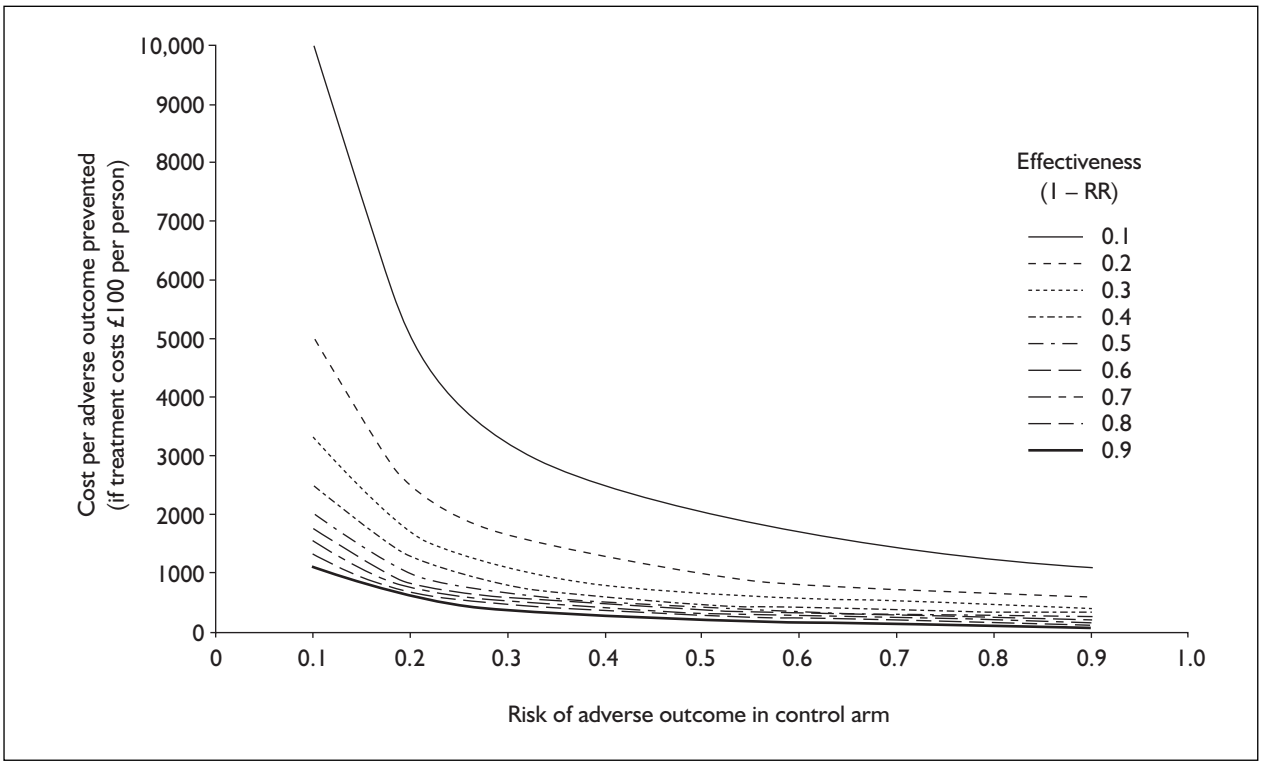


FIGURE 23 *Cost per disease outcome prevented (assuming cost of treatment = £100)*

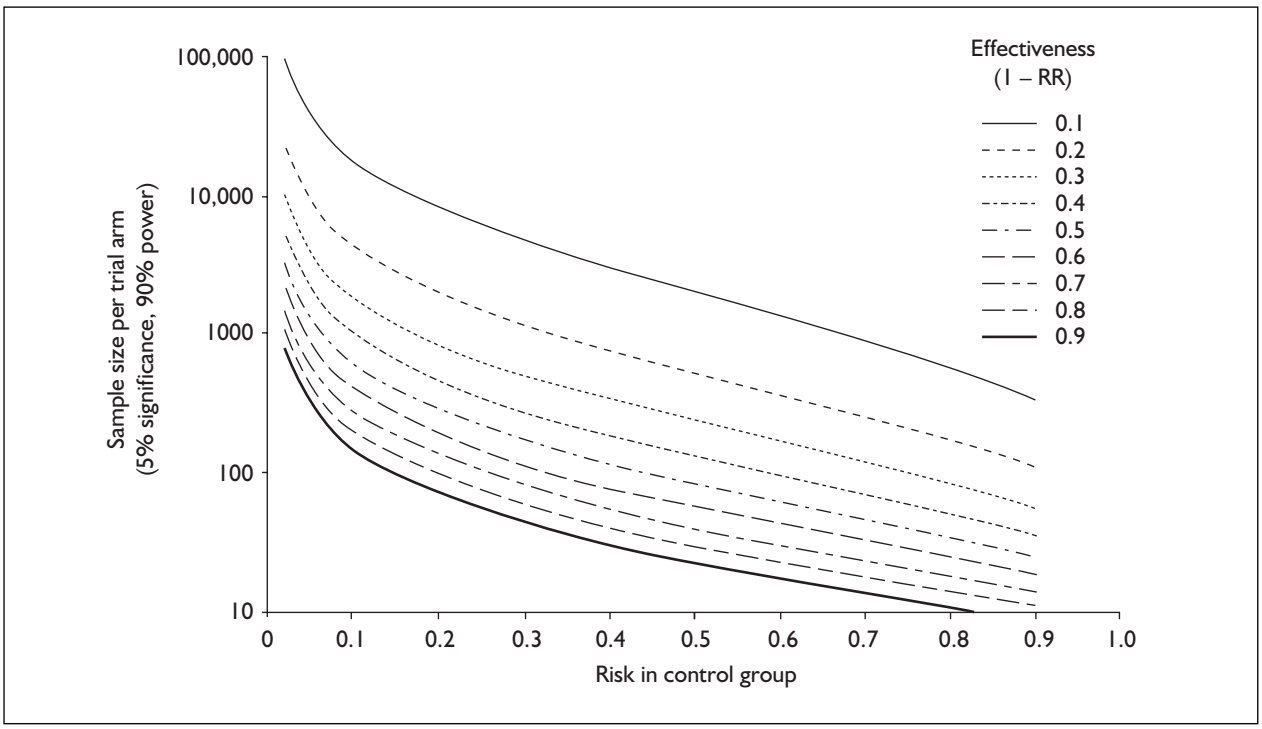


FIGURE 24 *Sample size needed in each trial arm (for 5% significance, 90% power)*

Statistical assumptions

If one assumes that the relative effectiveness of the intervention (expressed as 1 – RR) remains the same at all risk levels of disease outcomes in the 'untreated' state, then:

- Smaller sample sizes are required if lower risk populations are excluded, and larger sample sizes are needed if higher-risk populations are excluded (*Figure 24*).
- Conversely, for a given sample size, the power to detect a significant effect is lower if high-risk populations are excluded, and is higher if lower risk populations are excluded (*Figures 25* and *26*).
- The probability of not detecting a significant effect can be fairly high if the underlying risk is moderately low and if relative effectiveness is moderately low (*Figures 25* and *26*).

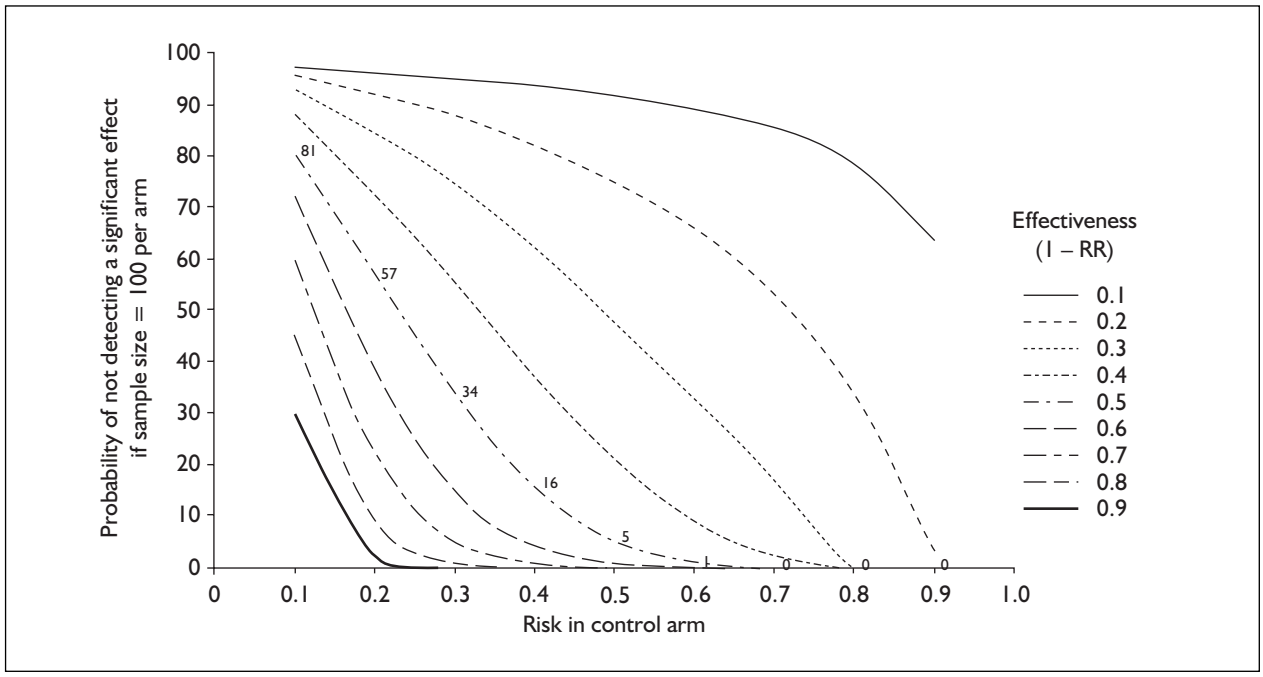


FIGURE 25 *Probability (%) of not detecting a significant effect (at 5% level if sample = 100 per arm)*

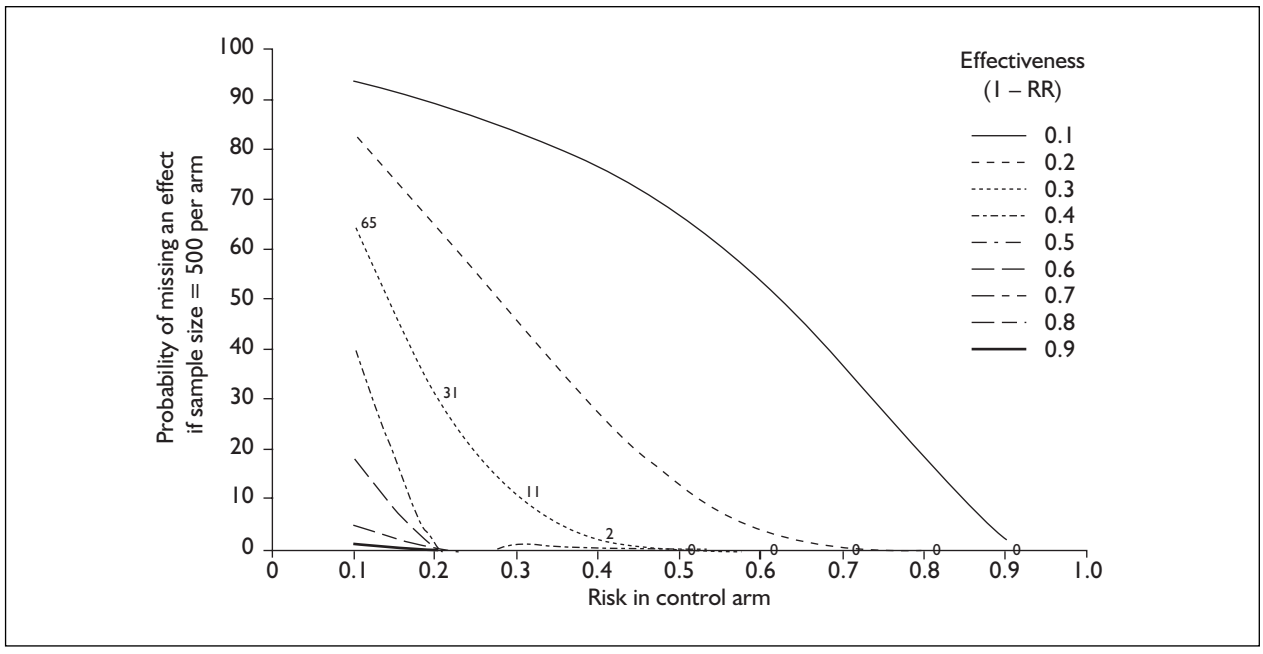


FIGURE 26 *Probability (%) of not detecting a significant effect (at 5% level if sample = 500 per arm)*

Discussion

Epidemiological and statistical considerations

A measure of absolute effect provides valuable information to the epidemiologist and policy maker, and is a vital complement to a measure of relative effect. Nevertheless, our models demonstrate that an overall or 'average' measure of absolute effect in a trial is, in statistical terms, strongly associated with the 'untreated' risk levels of trial participants in a way that a measure of relative effectiveness might not necessarily be. Hence, there might be situations where the absolute effectiveness and cost-effectiveness of a treatment could actually be underestimated in a trial owing to the exclusion or inadequate representation of a high-risk group, such as older people. Likewise, high levels of inclusion of a high-risk group would tend to increase the power of a study or conversely, reduce the sample size needed. One caveat to this general principle has been noted by Zelen: in cancer trials involving older people, the increase in non-cancer outcomes (i.e. non-contributory events) may reduce the power of cancer trials.[282]

Beyond the 'average effect'

However, if an intervention tended to produce undesirable side-effects, then a trial sample with many high-risk patients might not produce such an optimistic picture of outcomes. Conversely, a sample dominated by low-risk people might give a treatment a deceptively safe and risk-free appearance. Again, the 'average' absolute effect produced by the trial would be strongly dependent on the profile of the trial sample (unless the intervention produced side-effects at a constant absolute rate across all population groups, which might conceivably happen under certain circumstances). To evaluate accurately the balance of benefit and harm in low-risk or high-risk groups, one would have to depart from reliance on the average effect and examine benefit and harm within each group of interest. This would clearly involve a considerable expansion of sample size to provide adequate statistical power and precision to compare effectiveness and toxicity in subgroups of the population.[274] Such large numbers of patients could only be acquired through mega-trials or through individual patient data meta-analyses of trials.

Ethnic groups

We noted in Chapters 3 and 4 the lack of available data on how different ethnic groups fare in trials, and in Chapters 5 and 6, we were unable to comment on outcomes in the cohorts by ethnic groups, owing to lack of relevant data. In Chapters 7 and 8, we were at least able to cite cross-sectional survey results showing how the prevalence and nature of cardiovascular disease in England varies in men and in women according to their ethnic group. Although we cannot draw conclusions about the effectiveness and toxicity of our exemplar drugs, statins and NSAIDs, by ethnic group, a case could be made for regarding some ethnic groups as high-risk groups in cardiovascular terms, for example, Bangladeshi men. Therefore, in theoretical terms, at least, a trial sample of a cardiovascular drug intervention in which Bangladeshi men were greatly underrepresented might underestimate the absolute effectiveness of that drug; this, of course assumes that the drug would produce the same RR reduction in Bangladeshi men as in other men, something which, unfortunately, the trials do not tell us.

Our lack of sound knowledge about risks and outcomes in ethnic groups in the UK is also a reminder about our even greater lack of knowledge about how interventions trialled in developed countries might work beyond those settings, in developing countries and 'middle-income' countries, and of how benefits and harms might vary in such countries by population group.

Conclusions

Measures of absolute effectiveness are necessary for analyses of benefit and harm and of cost-effectiveness and are vital complements to measures of RR. Yet absolute effectiveness is inextricably linked to the underlying level of risk of disease events, which can vary greatly across different population groups, for example between men and women, and between the young and old. We have demonstrated statistically and graphically that measurements of absolute effectiveness and cost-effectiveness will be misleading if different population groups are not adequately represented in trials. The most useful information would come from estimation of absolute effect within population groups, where possible, which would require very large sample sizes.

Summary: epidemiological and statistical assumptions about trial exclusions

- Measures of absolute effectiveness are vital complements to measures of RR.
- Measurement of absolute effectiveness is necessary for informative analyses of benefit and harm and of cost-effectiveness.

- Absolute effectiveness is statistically dependent on the rate of disease events in the 'untreated' state (the underlying risk of events).
- Underlying risk of disease events will tend to vary by population groups.
- In CVD, as in many other diseases, older people could be described as a 'higher risk' group and younger people as a 'lower risk' group.
- Some ethnic groups in the UK could be classified as high-risk groups in cardiovascular terms.
- We explored in statistical models how absolute effectiveness in trial samples varies between groups according to their underlying level of risk of disease events.
- We demonstrated graphically that exclusion of high-risk populations from trial samples will result in an underestimation of absolute effectiveness and of cost-effectiveness.
- We demonstrated graphically that exclusion of low-risk populations from trial samples will result in an overestimation of absolute effectiveness and of cost-effectiveness.
- The inclusion of high-risk people could, in theory, increase the power of a trial or enable sample size to be reduced.
- If a treatment tends to produce adverse events, the rate at which these are produced in a trial will depend on the proportion of high-risk people in the sample.
- Measures of absolute effectiveness and cost-effectiveness will be misleading if different population groups are not adequately represented in trials.
- The most useful information would come from estimation of absolute effect within population subgroups, which would require very large sample sizes.

Chapter 13

Observations on diversity

Introduction

In the subsequent, final chapter, we state the conclusions from our enquiry into the causes and effects of socio-demographic exclusions from clinical trials and make recommendations for future research. It became apparent to us, however, while conducting the specific investigations that we have reported here, that our project covered an important but restricted part of an expansive field. This field must, of necessity, be described as complex because of the diverse nature of healthcare interventions, the diversity of the types of trial that can be carried out and the diversity of the people with need for healthcare. A given trial could be conceived of as having a specific location in this web of diversity, the location being defined by the type of intervention, the type of trial and the type of individuals in the trial sample. Hence the effect of exclusions on the external validity of a given trial might depend on its location in this web.

Our project encompassed randomised trials of two classes of pharmacological agent, both strongly promoted by researchers and manufacturers, designed to meet important health needs in large numbers of people, but conducted in relatively restricted samples. Although we believe that our findings have some implications for all trials, in this penultimate chapter we give an overview of the different diversities that interweave to make up the wider web.

The diversity of interventions

A classification of the different purposes of intervention and modalities of healthcare intervention is proposed in *Table 32*. Drugs represent just one modality, but the pharmaceutical agenda continues to dominate clinical trials and the work of trialists, in spite of increasing recognition of the contribution of non-drug interventions in healthcare.[191,256] A complex intervention combines two or more modalities of intervention. Strictly speaking, nearly all interventions have some characteristics of the complex trial, as they involve 'context effects', such as those arising from the beliefs and approach of the prescriber, any advice and suggestions for behavioural change, the attitudes of the patient and whatever pill, physical device or operation that might be deployed.

It is clear that socio-demographic exclusions affect the generalisability of data obtained from drug trials, the dominant form of researched intervention. Age clearly affects drug effects, principally through changes in renal and hepatic metabolism, a measurable effect of biological age, rather than chronological age; our findings with NSAIDs confirm this. Our finding that sex or gender (we do not know which) affects susceptibility to NSAIDs is new, and raises the possibility that other drugs have as yet undiscovered different effects in men and women. Further research should be undertaken to explore this finding. Debate is continuing on the subject of the degree to which pharmacological agents are metabolised differently according to a person's ethnic background (or, to be more exact, according to the genetic correlates of their ethnic background).[283] It is by no means generally accepted that drugs have equivalent effects in people of different ethnic backgrounds.

It would seem to be a reasonable working hypothesis that low levels of inclusion according to

TABLE 32 *The diversity of interventions*

Purpose of intervention	Modalities of intervention
Primary prevention	Pharmacological
Secondary prevention	Surgical
Symptomatic	Physical interventions and 'devices'
Palliative	Educational and behavioural
Diagnostic	Psychological
Screening	Complex (an intervention combining modalities)

age, sex or ethnic background will influence generalisability more in trials of psychological interventions or interventions involving an element of education or behavioural change than in trials of drugs. For example, an attempt to change patterns of smoking, drinking, eating or exercise may have different implications and consequences for different people according to their social, religious or cultural background.

It also seems likely that agreement to take part in trials also differs according to age, sex and ethnicity, and that this would vary according to the type of intervention being tested. An aspect of the complexity of inclusion and exclusion from trials that we have not been able to address, but would appear fundamental, is differences in the willingness to be involved in research involving different types of intervention according to socio-demographic status. For example, in a recently established trial of treatments for prostate cancer, reluctance of younger men to be randomised was dependent on the way in which information was presented to them at trial recruitment.[284] An associated problem in need of research is the potential barriers and facilitators to the involvement of minority groups and older people. It may be that there are relatively simple ways of improving inclusivity that have been applied in the NHS to improve access to services by minority groups and might be evaluated in the context of recruitment to RCTs.

The diversity of trial types

There exist several major classes of trial, which are usually described simply as Phase I, II, III and IV. This terminology is universally used in pharmaceutical trials and widely applied in other contexts. However, it is often used differently by trialists from different disciplinary backgrounds, working in different clinical contexts and concerned with different kinds of interventions. It is therefore inadequate for universal use without further clarification.

Phase I trials generally only pertain to pharmacological agents and to a limited extent to medical 'devices'. Phase I trials are specifically designed to measure the distribution, metabolism, excretion and toxicity of a new drug. Since many devices also require a surgical intervention, the term Phase I trial would not normally be used to describe the early development phase of such interventions. Rather, surgical techniques, behavioural interventions and complex packages of health service interventions tend to be developed by interested experts during their routine clinical practice. Assessment of these technologies is likely to be achieved through clinical audit and small-scale observational studies. In pharmacological studies both *N*-of-1 trials, in which a volunteer is subject to increasing dosages of a drug according to a predetermined schedule, and small-scale uncontrolled trials of patients with the condition, are used. Since these studies are generally uncontrolled in their design, selection bias is not usually considered a problem by the investigators. Biological differences where they exist, however, may have considerable scientific impact. Such differences could conceivably correlate with age, sex or ethnicity.

Phase II trials are designed to test the feasibility of and level of activity of a new agent or procedure. In particular, they are used to determine the safety and efficacy of the agent or intervention and to determine the logistics of delivering the intervention including an estimate of the direct cost to the service provider. Phase II trials are used in feasibility studies of pharmacological agents, devices, surgical techniques and physical and behavioural therapies. Studies are usually small and uncontrolled prospective studies that focus on short-term intermediate outcomes. As with Phase I trials, selection bias is not usually considered a problem. Phase I and II trials are not hypothesis driven in the sense that formal comparisons are made with other treatments or interventions and therefore do not usually determine the experimental design.

Phase III trials, however, provide a full-scale evaluation of the treatment or intervention and are designed specifically to estimate the relative efficacy or clinical effectiveness against a standard, alternative or placebo treatment by comparing efficacy against defined clinical end-points. A wider range of interventions may be subject to a Phase III trial including, in addition to those subject to Phase II trials, preventive and screening technologies. Phase III trials normally take the form of large randomised explanatory controlled trials with or without subgroup analysis and using defined primary and secondary clinical end-points or long-term outcomes.[285,286] Although a range of trial designs may be used, random allocation to an experimental or control group is a defining characteristic of Phase III trials. Selection bias is therefore an important issue since the aim of the trial will be to generalise more widely to the population at risk.

Overlap exists between Phase III and IV trials. In the evaluation of pharmacological agents, the Phase IV trial is often simply used for post-marketing surveillance with the purpose of estimating the frequency of uncommon clinical side-effects. Within the context of the pharmaceutical industry, Phase IV trials are often used to bring a new drug to the attention of a large number of clinicians, particularly in primary care. For a wide range of other health technologies, Phase IV trials are often described as complex trials designed to estimate the relative efficiency or cost-effectiveness of a treatment or intervention against a standard, alternative or in some cases a placebo by investigating clinical and cost-effectiveness against clinical and psycho-social end-points within the population at risk. Phase IV trials are normally large pragmatic trials that include defined clinical and psycho-social end-points and long-term outcomes, and include economic evaluation within the trial design.[285,286] Selection bias is an important issue and socio-demographic exclusions from the trial where they happen could limit its generalisability to the population at risk, impacting on the quality of the clinical and policy decision-making. The overlap between Phase III and Phase IV trials means that the types of design often merge and for some evaluations the objectives of the two phases are achieved simultaneously in the same trial design with the inclusion of subgroup analysis and explanatory analysis within pragmatic trial designs.

Randomised trial designs are also used in the evaluation of professional behaviour change where the purpose is to determine the cost-effectiveness of different implementation strategies. Such evaluations also use large randomised pragmatic trials with defined clinical and psycho-social outcomes for patients and behavioural outcomes for professionals. As with Phase III and IV trials, socio-demographic exclusion may compromise the generalisability of the results.

The dominance of classical, drug-based RCTs, and the phases described above, have been a development responding to the needs of the pharmaceutical industry and health professionals to test the huge numbers of new drugs that have appeared over the last 50 years. The classical placebo-controlled or comparative double-dummy designs are well suited to testing drugs, but are not so well suited to testing educational, behavioural or psychological interventions, or complex packages of care, where placebos and blinding may prove impossible. Cluster randomisation (randomisation by group rather than by individual), waiting list trials, preference designs, prerandomisation and other alternative designs have been used to try to deal with these methodological problems. It is important to note that the exemplars we used (statins and NSAIDs trials) were almost exclusively classical placebo controlled or equivalence RCTs within Phases III or IV of drug development, so they represent only part of the diversity of trials.

The diversity of individuals and social exclusion

One of the major challenges for modern evidence-based healthcare is to bridge the gap between group-derived data, which 'average' the responses of a group of individuals to any given intervention, and patient-centred healthcare, which recognises the individuality of each patient and of their own response.

Many of the variables can interact. For example, health beliefs may vary within different ethnic groups and in different age cohorts. Certain genetic characteristics may co-localise with race. Social disadvantage is more likely in older people and ethnic minorities. An examination of people who are socially excluded (those less able to participate in local culturally determined activities, including gaining access to healthcare) would complement the current research project. The complexity of issues surrounding age (chronological, biological and social), sex/gender and race/ethnicity was outlined in Chapter 2. Hence it would be difficult to create a single model of universal application, which quantitatively relates inclusion levels of socio-demographic groups in trials to the generalisability of those trials.

Figure 1 in Chapter 2 illustrates the overlap of age, sex and ethnicity. It is clear from the discussion above, that emerged from the workshops and discussions that took place as an integral part of this project, that the reality of the situation is considerably more complex.

Socio-demographic variables: cause or effect?

As explained in Chapter 1, we had hoped to develop a model of the causes and effects of socio-demographic exclusions from clinical trials as part of this project. The emerging complexity of the issues made that a seemingly impossible

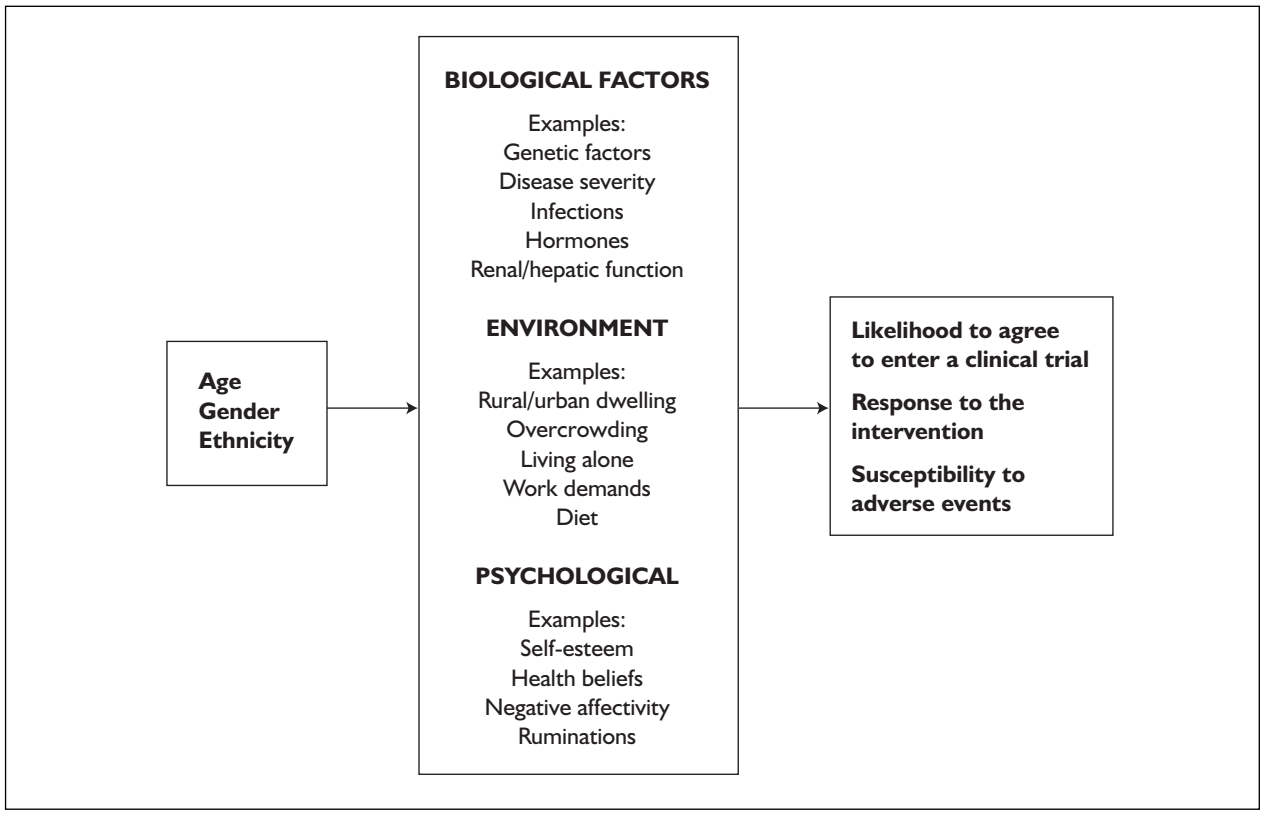


FIGURE 27 *A diagrammatic representation of some of the explanatory variables that may mediate the effects of age, gender and ethnicity on the external validity of clinical trials (adapted from Johnston* et al.*, 2002)*[287]

and irrelevant task. A further level of complexity is introduced if one considers how we deal with socio-demographic variables in medical research. Because they predict many diseases and responses to interventions, we tend to control for them. However, as pointed out by Johnston and colleagues,[287] this may result in our losing the ability to examine how they explain such variation. Johnston and colleagues propose the use of the sort of model illustrated in *Figure 27* to examine the possible causes of the interrelationships between socio-demographic variables and health, rather than controlling for them.

Conclusions

We concluded that our empirical research covered an important but restricted part of an expansive field. This field was complex because it was characterised by three major, interconnected variables, namely the range of types of healthcare interventions, the different types of trial that can be carried out and the range of people with need for healthcare. Each of these three variables could influence the relationship between levels of inclusion of socio-demographic groups and the generalisability of a trial. A given trial could be conceived of as having a specific location in this complex web of diversity. Hence it would be difficult to propose a single theoretical model of universal application which quantitatively related inclusion levels of socio-demographic groups in trials to the generalisability of those trials.

Summary of observations on diversity

- Our empirical findings from research into socio-demographic exclusions from clinical trials and generalisability were based largely on investigation of 'classical' RCTs of two commonly used drugs.
- We believed that some of our findings had implications for all trials, but realised that our empirical work covered a restricted part of an expansive field.
- This field was complex because it was characterised by three major, interconnected variables.
- These 'variables of diversity' were the different types of healthcare interventions (e.g. primary prevention, secondary prevention, drug treatment, psychological treatment), the

different types of trial that can be carried out (e.g. Phase I, Phase II, Phase III, Phase IV, individual randomisation or group randomisation) and the diverse range of people with need for healthcare (e.g. men, women, children, older people, ethnic minorities, the disabled and socially excluded).
- Each of these three variables could, in theory, determine the relationship between levels of inclusion of socio-demographic groups in a trial and the generalisability of the trial.
- Any given trial could be conceived of as having a specific location in this web of diversity.
- Consideration of the three variables suggested some situations in which the generalisability of trials would, in theory, be severely compromised by low levels of inclusion of different socio-demographic groups, such as with psychological interventions.
- Yet it would be difficult to propose a single theoretical model of universal application which took account of the three major variables of the causes and effects of socio-demographic exclusions from trials.

Chapter 14

Summary, conclusions and research recommendations

In order to provide safe and effective interventions for individuals, we need evidence that is both reliable and valid. This is most easily produced by undertaking trials in samples of people who are as homogeneous as possible to reduce variability and applying the results in similar, well-defined groups of patients. However, in order to be equitable, we also need to be able to provide appropriate care for everyone in the very heterogeneous community served by the NHS. This tension between scientific evidence and distributive justice is at the heart of this research project.

The main purpose of the commissioned research was to explore the possible effects of socio-demographic exclusions from trials on external validity. We have completed work on this, using two drug exemplars. However, we also widened the research brief to look at wider, contextual issues. As described in Chapter 1, we carried out an exploration of the social, legal and ethical factors behind trial exclusions, comparing the UK with the USA. This part of the work examined the factors lying behind these exclusions and their implications for distributive justice.

The ethical background is covered in the first part of Chapter 2. Based on literature reviews and a series of workshops with key stakeholders, our main conclusion was that issues of justice in medical research have received much less attention in the UK than in the USA. The commissioning of this research by the HTA provides one indication of emerging awareness of the importance of the issue, but we found few others. Whereas legislation has had to be passed in the USA to ensure that issues of inclusivity are taken seriously.

> Conclusion 1. There is a need to increase awareness about the importance of equity and inclusivity in some of the UK health research community. Greater inclusivity in trials is desirable to ensure the generalisability of the data to patients who will use the intervention.

We would not argue that the UK needs to follow the USA in introducing legal requirements to enforce inclusivity. But we do believe that guidelines for commissioned research, for the conduct of clinical trials and for the practice of ethics committees should include advice on these issues. These guidelines should recommend the inclusion of women, older people and minority ethnic groups in samples in appropriate numbers and should also advise researchers to provide sound scientific reasons for any exclusions.

Our general conclusions on the exclusion of older people, women and ethnic minorities from trials and other clinical research projects in the UK are covered in the second part of Chapter 2.

We conclude that older people are systematically excluded from research in the UK, in spite of their being the main consumers of healthcare. The justifications given for this exclusion are generally related to the likelihood of co-morbidity, impending death or problems with consent or the likely toxicity of the intervention. However, we argue that that these rationalisations rarely stand up to serious ethical scrutiny. With regard to age and its influence on effects of treatments, there is a need to distinguish between biological mechanisms (e.g. drug metabolism), social circumstances (e.g. isolation resulting in lower adherence to treatments) and chronological effects (e.g. co-morbidities accumulated over time), which may all independently influence treatment efficacy. There appears to be confusion amongst some UK researchers about these differences between chronological, biological and social ageing.

There is less information available on the exclusion of women from research carried out in the UK. However, the fact that they make up the majority of older people in the population is clearly relevant here. There is also some evidence that younger women are underrepresented in research studies, for example in CVD. It appears that there is considerable confusion among UK researchers about the differences between sex and gender and, as in the case of ageing, this lack of conceptual clarity limits our capacity to make sense of any observed differences between women and men.[288]

We also explored the evidence indicating the underrepresentation of ethnic minorities in medical research in the UK. This appeared to result both from policies of deliberate exclusion (said to be justified because of language barriers) and from a failure to recognise the importance of inclusion. Again, this failure to include different groups was compounded by conceptual confusion. It is clear that cultural aspects of ethnicity may have major effects on health-related behaviours, including suitability and willingness to take part in trials. However, in a multicultural society such as contemporary Britain, an individual's sense of ethnic identity is affected by many factors and may be context related. The concept of 'race' seems largely irrelevant to modern biology, as more relevant information is provided by explicit genotyping, but at the same time racially linked genetic inheritance may affect responses to some interventions. Further work is needed if researchers are to make the best possible sense of these complex interrelationships between biological 'race' and social ethnicity.

In general, the exclusion from trials of those who are seen as 'different' or would require increased resources to be included (e.g. interpreters, home visits for older people) cannot be defended ethically and is against the principle of wide inclusion criteria to maximise generalisability of trial findings.

> Conclusion 2: Older people, women and ethnic minorities are often excluded from UK medical research studies. The reasons given usually relate to practical considerations, but they are often weak and inappropriate and there is generally no moral or ethical justification for these exclusions.

> Conclusion 3: The UK medical research community appears to be naïve about the significance of age, sex, ethnicity and social exclusion as variables in research. Chronological, biological and social ageing, sex and gender and race and ethnicity are rarely distinguished or given due consideration.

The empirical/statistical part of this project consisted of case studies of research on two drugs and this is presented in Chapters 3–11. The choice of drugs reflected our own research interests, but also provided evidence about a new class of drugs, statins, which has been subjected to recent, large, high-quality trials and saves lives. By contrast, NSAIDs have been in use for decades, trials tend to be smaller and of lower quality and their use is for symptom control.

The first part of our findings (Chapter 3) conformed to some of the expectations derived from our scoping exercise, as outlined in our next conclusion.

> Conclusion 4: Examination of the inclusions and exclusions from trials of statins and NSAIDs showed that inclusivity was greater in the USA trials than in other countries. In the UK, women were rarely included in statins trials, older people were under-represented in trials of both drugs and reporting of ethnicity is poor for trials of both drugs.

Many of the most important findings in the study concerned the disparities noted between trial populations, those in probable need of the treatment and those using the drugs in question (Chapters 9 and 10).

In the case of statins used to lower cholesterol for the secondary prevention of CVD, it is clear that both older people and women were under-represented in trials in comparison with the population in need. The mismatch for older people carries over into treatment in routine clinical care, since only about half of the older group potentially in need are receiving statins. Women represent 40–45% of both the 'with need' and 'on treatment' populations, but only 16% of trial subjects.

> Conclusion 5: Women and old people are under-represented in statins trials. Older people are not being treated as often as their need would predict that they should be, but this is not the case for women.

Ethnic minorities have variable susceptibility to CVD. Bangladeshi men in the UK, for example, have a much higher incidence of disease than other groups. In spite of this, ethnicity is rarely reported in statins trials undertaken outside the USA.

> Conclusion 6: Although South Asian ethnicity is an important risk factor for CVD disease in the UK, it is not clear what steps, if any, UK statins trialists have made to include such people from different ethnic groups.

In the case of NSAIDs, the drugs used to relieve the symptoms of musculoskeletal disease, the pattern of disparities was different. Women were well represented in trials, which also included many older people. However, the 'oldest, old' were not included in trials in spite of the fact that they are high consumers of NSAIDs. The most striking finding in the context of NSAIDs was the systematic exclusion of people who are known to be at risk of adverse effects of the drugs. As in the

case of the statins, ethnicity is rarely reported in trials.

> Conclusion 7: Women are adequately represented in NSAIDs trials, which have also included some older people, but not the 'oldest, old', in spite of their being a group that use these drugs extensively. People at risk of adverse effects from NSAIDs have been systematically excluded from trials, yet these people are particularly likely to receive NSAIDs in routine practice.

The consequences of these patterns of inclusion/exclusion were different in the two exemplars. In the case of the statins, where the data allowed us to calculate relative effects on external validity of effectiveness, we found no problem. Women and older people, when included in trials, apparently respond in a very similar way to statins as do the younger male group that is the predominant trial population.

> Conclusion 8: The exclusion of women and older people from statins trials does not appear to affect the external validity of the relative effectiveness data.

However, in the case of NSAIDs, exclusion of older people and those at risk of adverse effects appears to have had a major effect on our understanding of the toxicity of these drugs. Our findings on NSAID-associated toxic events are particularly noteworthy. Over recent years, most of the emphasis has been on gastrointestinal adverse events, in spite of the fact that the potential for renal toxicity has been known about for just as long. We found that toxicity from renal events was more frequent in association with NSAIDs prescribing than GI events. It has long been known that older people are more susceptible to adverse events, and our data confirm this. In addition, we have made the original observation that men were more susceptible than women to both renal and GI events.

However, it is also clear that those older people who do become included in trials are unlikely to be representative of all those in their age group who are likely to take the intervention in the community. Clearly, such a problem could affect our findings and could invalidate the finding of differential toxicity of NSAIDs in men and women.

> Conclusion 9: Serious renal adverse events associated with NSAIDs prescribing are more frequent than GI events, although the latter have received much more attention in recent years. We believe that trial exclusions and the poor reporting of adverse events in trials more generally are partly responsible for the relative lack of recognition of the importance of renal toxicity arising from NSAIDs.

> Conclusion 10: We have confirmed the increase in susceptibility of older people to adverse events from NSAIDs and found, for the first time, that men are relatively more at risk than women.

> Conclusion 11: In the case of NSAIDs, the exclusion of older people and those at risk of adverse effects has affected the extent to which side-effects reported in clinical trials are relevant to the general population.

In the search for safer NSAIDs, it would be expected that people at risk of adverse effects would be included in trials to determine whether newer drugs are safer than the older ones. Obviously, close monitoring of physiological measures of renal function and symptoms and signs of GI disturbance would be required to safeguard participants. A more ethical trial design might be to compare new, apparently safer NSAIDs with simple analgesics such as paracetamol in populations who are at risk. This approach has the advantage of measuring both the benefits and the risks from a new NSAID without exposing vulnerable patients to the known risks of the older NSAIDs. Such arguments are equally applicable to the new coxibs as to the older NSAIDs that were the focus of this investigation.

In the case of both statins and NSAIDs, it does appear that trialists, particularly outside the USA, have been operating within the protectionist/paternalistic paradigm, and not considering inclusivity when designing and reporting on their trials.

The **methodological aspects** of this work are important. Conventional evidence-synthesis techniques can allow estimates of the effects of exclusions on effectiveness to be calculated, as in the statins example, although trial meta-analysis raises potential problems with the quality assessments for inclusion, and meta-regression cannot be applied. Individual patient meta-analysis may be the best way to do further work of this sort, but this is very time consuming, difficult and expensive to undertake. In the case of NSAID toxicity, the conventional trial data and evidence synthesis approaches are not applicable, and we were only able to detect the problems arising from trial exclusions through the analysis of a large prescribing database. Massive, highly inclusive trials of long duration would be the only way to detect such problems earlier, but such an approach is unlikely to be feasible.

> Conclusion 12: Conventional trials and techniques of synthesising the evidence from them can allow estimates of the effects of socio-demographic exclusions on relative effectiveness to be calculated, provided that large numbers of patients have been entered into trials. In the case of adverse effects, these approaches may not be sufficient, and massive, long-term totally inclusive trials would be needed to detect problems.

We were only able to carry out this work because we had access to large databases, including the MEMO study with its unique (for the UK) database of individual dispensed prescribing that can be record linked to other information such as hospital admissions. It is currently difficult to apply the same techniques in other cases in order to assess the effects of trial exclusions on external validity, simply because of the absence of appropriate large datasets. However, record linkage in the entire population of Scotland (five million people) is already technically feasible and all that is required is the creation of a record linkable national prescribing register. In other parts of the UK record-linkage is more challenging but still technically achievable, although current interpretations of the need for informed consent for such linkages may hinder progress.

> Conclusion 13: Large amounts of data are needed to carry out analyses of the effects of exclusions on external validity. The UK has the capacity to use routine data for very large pragmatic trials but this potential will not be realised with current information systems.

We believe this raises important issues. Many aspects of HSR, such as quality assessment, are difficult in the UK because of the absence of good information systems in the NHS. In addition, recent European legal developments that make record linkage more difficult could make it even harder to set up databases and record linkage systems to improve the situation.

The average effect estimated in a trial, the 'headline' measure of RR or RR reduction, will sometimes be a generalisable measure of the therapeutic outcome. We observed such a situation in the case of statins and it is likely that this will occur in the case of other highly effective treatments. However, such a situation is, of course, unpredictable, and RRs of adverse events may not be uniform throughout the population, as we observed with NSAIDs.

As argued in Chapter 13, estimates of absolute effects, such as the NNT, which take account of the natural event rates, are preferable to the relative effects estimates of either benefit or harm arising from conventional trials, particularly for the evaluation of cost-effectiveness. In most conditions, natural event rates will vary in frequency in different socio-demographic groups. In Chapter 13 we modelled the effects of the inclusion or exclusion of those at relatively high or low risk on the estimates of the absolute effects, cost-effectiveness and power calculations in clinical trials. The models show that trial exclusions could lead to major over- or underestimation of the effects of an intervention if reliance is placed solely on trial data to determine NNTs and cost-effectiveness of treatments for groups that are inadequately represented in such trials. The use of large prospective observational databases may be helpful in deriving NNTs by application of trial RR reductions to the absolute risks experienced by population subgroups of importance.

> Conclusion 14: Measures of absolute effectiveness (e.g. NNT) and cost-effectiveness differ according to the varying levels of risk in different groups of people that might be represented in trials.

In Chapter 13, we further considered the complexity of the issue of the causes and effects of socio-demographic exclusions from clinical trials. During the workshops and discussions held around this project, the 'web of diversity' emerged as an important theme. It was recognised that when the diversity between different types of interventions and different phases and designs of trials were set alongside the marked differences between individuals and groups in both access to research and responses to interventions, the resulting picture was one of massive complexity. As a result, no simple over-arching model of the interaction between these different factors could be developed.

> Conclusion 15: Age, sex and ethnicity are only three of many interrelated variables that can affect the causes and effects of exclusions from clinical trials. Any single exemplar sits within a 'web of diversity' of types of intervention, trial phases and trial designs and variations between individual participants and groups.

Our findings also highlighted the extent to which age, gender and ethnicity may be related to social exclusion and the importance of considering the factors promoting and hindering access to clinical research and trials amongst different groups in the population.

> Conclusion 16: Socio-demographic factors may be linked to social exclusion and more research is needed

on the barriers preventing minority and disadvantaged groups from being included in medical research.

We believe that trial populations should better reflect those who use the intervention being tested (and the way they use it) than is usually the case at present. In an ideal world, trial populations would reflect all those in need of the intervention being tested, but such an ideal is unlikely to be attainable in most instances. All trial reports should include clear reporting of the inclusion and exclusion criteria to make it easier to interpret the likely level of generalisability of the data. Any reasons for specific exclusion (or overinclusion) by age, sex or race also need to be stated and justified scientifically and ethically.

Conclusion 17: Populations included in clinical trials need to be more representative than they are at present.

Recommendations for further research

We believe that our findings have as many implications for policy change as they do for further research. We have five recommendations for further research, presented here in our priority order:

1. Our findings highlight the research problem of either answering a specific question about an intervention (which might require very homogeneous trial populations) or providing data or direct relevance to health services such as the NHS (which might require different trial designs and inclusions and a more pragmatic approach). There is at present no clear answer as to how this issue should be resolved. We suggest a multi-disciplinary research project, with consumer involvement, to examine this and come up with recommendations on this aspect of the future conduct of clinical trials. Such work could include HTA-commissioned research and, if successful, might guide both commissioning and monitoring of future research.
2. It is clear that the meaning, measurement and reporting of socio-demographic data, including age, sex and ethnicity, are not well understood by all UK medical researchers. We believe that there is a pressing need for new research on these issues with a view to developing appropriate guidelines and recommendations.
3. The reasons for exclusions from trials need to be understood better. More work is needed to uncover the barriers and facilitators to the involvement of all population groups in clinical research. This will provide the basis for improving patterns of inclusion.
4. One of the most surprising, original findings of this work is the sex difference in the susceptibility of people to adverse events when taking NSAIDs. We have not been able to examine the causes for this difference, which could relate to sex (biology), gender (social identity) or a mixture of the two. We believe that this should be explored through further research.
5. Our work has also highlighted the problem of the paucity of good, large databases capable of linking prescribing to outcomes in the UK. This, we believe, is a major problem for all forms of health services research. Research on how Section 60 of the Health and Social Care Act 2001[289] is being applied to the use of patient-identifiable information in the establishment and use of disease and other registries would be helpful in developing current policy. Furthermore, there is no easy way of finding out what databases are available. Current work conducted by the NHS Information Authority in this area appears to be confined to issues of confidentiality of patient information and to cancer registries. We suggest further research to develop a 'register of registries and databases' to explore how information systems in the UK could be improved and to promote collaboration between researchers in this field.

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Contribution of authors

The project was designed by the seven main authors, with help from the 'initiation' collaborators listed above. Paul Dieppe was principal investigator and Chris Bartlett acted as project and report coordinator. The seven main authors contributed to analyses and drafting and approved the final report. The qualitative work in Chapter 2 was performed and the text drafted by Lesley Doyal. Max Bachmann devised and drafted Chapter 12.

In Chapters 5 and 6, Li Wei (for statins) and Steve Morant (for NSAIDs) performed the statistical analyses and wrote initial drafts and are therefore credited as co-authors for those chapters. John Bond, David Badcott, and Helen Lambert made important contributions to Chapters 13 and 14 and are credited as co-authors for those chapters. Affiliations of these chapter-contributing writers are as follows: Li Wei and Steve Morant (c/o MEMO, University of Dundee, UK), John Bond (Centre for Health Services Research, University of Newcastle, UK), David Badcott (Centre for Applied Ethics, Cardiff University, UK) and Helen Lambert (Department of Social Medicine, University of Bristol, UK).

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Appendix 1

Topics presented at three workshops held to support and inform the 'exclusions' project

Barriers to clinical trials in older people

MRC Health Services Research Collaboration, Department of Social Medicine,
University of Bristol
May 2000

Main Speakers and Topics

Prof. Carol Jagger **Department of Epidemiology and** **Public Health, University of Leicester**	*Older people are excluded from trials*
Dr Rod Taylor **National Institute for Clinical Excellence,** **London**	*The Relenza story*
Prof. Cameron Swift **King's College, London**	*The necessity for involvement of older people in clinical trials*
Prof. Len Doyal, **Barts and RL School of Medicine and Dentistry,** **University of London**	*Medical research, injustice and the elderly*
Dr Jackie Brown **MRC HSRC, University of Bristol**	*The health economist's perspective*
Dr Mike Clarke **Clinical Trial Service Unit/UK Cochrane Centre,** **University of Oxford**	*Should older people be included in clinical trials*
Dr Max Bachmann **MRC HSRC, University of Bristol**	*Why older people should be excluded from trials*
Dr Matthias Egger **MRC HSRC, University of Bristol**	*Why, when, and how older people should be included in trials*
Dr Richard Lindley **Edinburgh**	*What are the main likely reasons for exclusions?*

Carol Jagger. Older people are excluded from trials

There are few diseases or conditions that present for the first time in later life and therefore few treatments prescribed solely to older people. Although there is no clear cut-off to define 'old age', the increasing likelihood of concurrent illness and greater mental and physical frailty with ageing means that older people may be inherently different to younger adults in the way in which they metabolise drugs.

Professionals caring for older people need a firm evidence base on which to base their decisions, although this is lacking for many aspects of care. Even for treatments of diseases and conditions that are seen predominantly in later life, there are few trials with sufficient numbers of older people, particularly the 'oldest, old', to provide evidence of efficacy. For example, in Parkinson's disease, where prevalence increases with age and incidence peaks between 70 and 80 years of age, a recent review found only 38% of trials included subjects over 75 years of age.[1] Similar results have been found for reviews of trials in acute MI.[2]

Although older people are still being excluded from trials on the basis of age alone,[3] implicit exclusion is also common, through the application of other eligibility criteria such as the presence of co-morbid conditions. Eligibility criteria are often present in an attempt to produce homogeneous populations in which the benefit is likely to be the greatest, to maximise the possibility of detecting significant treatment effects.[4] However, a truly homogeneous population does not exist since even subjects who are the same on important baseline prognostic variables will still vary in the course of their disease and on unmeasured factors. Hence the gain in attempting to study a group of homogeneous patients may be outweighed by the loss in generalisability and clinical applicability of the results.[5]

Certain recruitment methods may result in study populations with few older people or unrepresentative of the general population likely to be treated. In these cases it may be difficult for the clinician to be aware of the paucity of older people studied, resulting in the late recognition of serious side-effects when drugs tested on predominantly younger adult populations are finally released and prescribed to larger numbers of older people. Clinical trials are likely to involve more regular monitoring and follow-up assessments than would routinely take place in practice and this in itself may be too burdensome for older people who may have other health problems or lack access to transport.

Gaining informed consent may also be a barrier to recruiting sufficient numbers of older people into trials. The clinical trial design is complex and, even if explained carefully, may not be understood fully enough to give true informed consent, particularly since terms such as 'trial' and 'random' may have different meanings to lay and professional groups.[6]

However, the increasing prevalence and incidence of dementia with advancing age are more of a concern for gaining informed consent for trials, and in particular trials of treatment for dementia.

It is usual to use proxies to obtain informed consent on behalf of the dementia patient, but rather than immediately approaching a proxy for consent, it may be best to promote a more pragmatic view of decision-making capacity in that if an individual appears competent then they are.[7]

Even without explicit exclusion of the basis of age alone, older people may fail to get through each stage of a trial: eligibility, recruitment, gaining informed consent and follow-up. Box 1 shows some important features that should be considered when designing trials of future therapies that may ultimately be used by large numbers of older people, so that in future, those responsible for the treatment of older people will be able to practise evidence-based healthcare.

BOX 1 *Design considerations to aid recruitment of older people into trials*

- Aim for as wide eligibility criteria as possible to ensure smaller random error, a wider applicability of results and a greater opportunity to test preplanned subgroup hypotheses.
- At the design stage, agree a list of strategies for recruiting specific subgroups (the very elderly, ethnic minorities) if these become underrepresented during recruitment.
- Regularly monitor the characteristics of subjects enrolled to ensure good representation of the general population.
- Give careful thought to the information to be given to subjects and the method by which it will be given, to gain informed consent. Consider whether and when consent will need to be obtained from a proxy.
- If possible offer home assessments or, where this is impossible, provide transportation to clinics at times convenient to the subject and their caregivers.
- Design a realistic withdrawal rate into the sample size calculation.

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Rod Taylor. The Relenza story

Background

Zanamivir is the first of a new class of drugs (neuramidase inhibitors) that selectively inhibit both influenza A and B neuramidases, essential for viral replication. Zanamivir was approved for licence in September 1999 and is taken by inhalation (two doses per day) using a breath-activated device for a five-day period. In July 1999, the Department of Health asked NICE to undertake a rapid appraisal of Zanamivir to inform the NHS policy for the approaching flu season.

The evidence base

A systematic review of the evidence of the clinical and cost-effectiveness of Zanamivir for the treatment of influenza was undertaken which included a detailed review submission from the manufacturer (Glaxo Wellcome). This review identified 11 RCTs. Eight of these were excluded from the review on the grounds that they were dosing studies, experimental induced flu or prophylactic studies. The remaining three trials were assessed to be of high methodological quality and pooled their data across a total of 1167 patients. Of this number, only 75 (4.5%) were aged ≥75 years and 217 (13.7%) of other high-risk categories (e.g. immunocompromised, history of asthma or CHD).

The findings

In the overall intention-to-treat patient analysis, Zanamivir reduced the time to alleviation of symptoms compared with placebo by a median of 1 day (95% CI 0.5 to 1.5 days). There was also a significant reduction in both influenza complications and antibiotic usage. None of these differences were significant in the subgroup analysis of elderly or high risk. Overall the cost in incremental cost-effectiveness ratio for Zanamivir was £7.41 per symptom-free day.

Implications

The trial evidence demonstrates Zanamivir to be effective in reducing symptom burden in generally healthy populations. Although not explicitly excluded from trials, only a very small proportion of those patients who are at highest risk from influenza infection, that is, the elderly and those with co-morbidity, were recruited.

Given both its relatively modest 'health benefits', insufficient evidence in older and other high-risk groups and the potential (and unknown) impact on primary care, NICE recommended that Zanamivir not be made available by the NHS for the flu season 1999–2000.

Trials of Zanamivir in the elderly have been under way since 1997. NICE is to reappraise Zanamivir in July 2000. NICE's future assessment of the clinical and cost-effectiveness of technology is going to be dependent on the availability of pragmatic designed trials recruiting the appropriate groups of patients (such as older individuals).

Cameron G Swift. The necessity for involvement of older people in clinical trials

Regulatory requirements for the inclusion of older people in clinical premarketing drug development studies were established in the UK in the 1980s and agreed internationally in 1994.[1] It is therefore surprising that surveys of Phase III clinical trials show continued and progressive under-representation of this age group.

The reasons for inclusion may be summarised as follows:

- demographic structure and drug utilisation
- history and epidemiology of adverse drug reactions
- age-associated change in physiology and pharmacology
- the benefits of a growing efficacy evidence base.

These constitute a continuing imperative.

Demographic structure and drug utilisation

Prescriptions per head in the UK have shown a continuing steady rise over the last two decades that is almost exclusively attributable to recipients of pensionable age and over.[2,3] This is a key market for the pharmaceutical industry and of major importance in terms of cost–benefit assessment for consumers and the health service. The scale of use alone would justify thorough clinical evaluation. However, evidence over the years (both epidemiological and anecdotal) has delineated a catalogue of examples of prescribing inappropriateness. Much of this is directly due to lack of experimental evidence from clinical evaluation in the relevant older patient populations. Examples have included neuroleptics, diuretics and NSAIDs.

History and epidemiology of adverse drug reactions

There is ample evidence that increasing age confers increasing susceptibility to adverse drug reactions.[4] Data from spontaneous adverse drug reaction reporting systems,[5] record-linked prescription event monitoring systems,[6] case cohort[7] and case–control[8] studies have consistently shown this for NSAIDs. Earlier prospective drug surveillance studies demonstrated the same for central nervous system drugs[9] and for the incidence of adverse drug reaction in general as a contributor to hospitalisation.[10] Furthermore, the dose-dependent nature of a majority of such adverse drug reaction (i.e. independently of the extent of prescribing) is clear from the data. Even these studies have tended to focus on serious adverse drug reaction and probably constitute a considerable underestimate of the true scale of insidious drug-related morbidity. Much of the latter goes unreported or unmeasured, particularly in very elderly people with co-morbidity.

Age-associated change in physiology and pharmacology

The introduction of a regulatory requirement for the inclusion of age-related data has more than justified itself by the knowledge gained. The influence of age (and some age-associated disorders) on drug pharmacokinetics is far better delineated,[11] although generalisation even to related drugs within a class requires caution. Age predictably reduces renal clearance and, less predictably, hepatic biotransformation, distribution into body water and albumin binding. Distribution into body fat and alpha-1 acid glycoprotein binding may be increased. Perhaps more importantly, age may alter drug pharmacodynamics,[11] either as a consequence of reduced homeostatic reserve capacity (e.g. postural stability, orthostatic blood pressure regulation, cognition, gastric mucosal defence mechanisms) or altered primary sensitivity to drugs (e.g. benzodiazepines, beta-adrenergic modulators). Much of this evidence has been derived from clinical studies of Phase I trial type. Problems with a number of compounds during the postmarketing period have been traceable to failure to delineate such changes adequately during drug development. More positively, the way has been paved for the potential development of compounds specifically tailored to older recipients.

The benefits of a growing efficacy evidence base

The more recent inclusion of older subjects in well conducted Phase II and III clinical trials has shown (in some cases unexpectedly) their capacity to benefit from drugs at least as much as younger subjects (or more so). Well-known examples include the treatment of mild-to-moderate hypertension;[12] thrombolysis,[13] ACE inhibition[14] and lipid lowering[15] after MI; and thromboprophylaxis in atrial fibrillation.[11] The emergence of the first useful symptomatic treatment in Alzheimer's disease (cholinesterase inhibitors) is directly due to rigour in the design (including the selection of older subjects) and conduct of clinical trials. Where there is a strong background of clinical trials evidence, more economic research strategies (e.g. prospective cohort studies[16]) may later be legitimately considered in establishing the overall effectiveness of drug therapy more widely in the older population.

Because of a range of special constraints affecting research with older people and the necessity for ethical and methodological rigour, there are strong arguments for basing this research predominantly or exclusively in units specialising in age research.

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Len Doyal. Research, injustice and the elderly

It can be argued that all citizens have an equal right to good healthcare. Physical and mental health are basic human needs. Without optimal participation in social life, individuals are harmed through not being able to reap fully the benefits of such participation. It is from others that we learn the cognitive, emotional and practical skills which make up our individual identities and potential for further social success. Hence to the degree that our physical and mental health are limited by disease and illness, so will our capacity to flourish as individuals. This will be so, irrespective of our age. Indeed, because of the potential in old age for social isolation, poor health as a block to optimal social participation can be especially devastating.

If physical and mental health are basic needs for everyone, then the same can be said for the healthcare required to satisfy those needs to optimal levels. Hence all individuals need access to care which minimises those aspects of illness that harm them through limiting their potential for social participation and for personal flourishing. Of course, the impact of such care will differ between individuals. Yet individual inequalities in capacity for good health do not entail an unequal need for good healthcare. Every individual – irrespective of age – has the same need for healthcare which is optimal for them.

The importance of mental and physical health as preconditions for optimal social participation, along with individual access to appropriate healthcare, constitutes the moral foundation for the belief in the right to such healthcare. There are two powerful arguments which justify the existence of both the right to optimal healthcare

in general and of the right of the elderly to have equal access to it.

On the one hand, rational self-interest dictates belief in such a right. Given our need for good healthcare, we never know when or at what age we might become ill and require it in the future. The only way in which we can assure ourselves access to such care is to endorse the equal right of everyone to it, irrespective of any personal attribute – including age – which some may argue should limit such access. On the other hand, to the degree that we believe that everyone has an equal duty to be morally worthwhile in our terms – to be what we would regard as a good citizen – then this desire commits us to helping them to do their best to do so. Since people will not be able to do their best without optimal physical and mental health, it follows that we have a duty to respect the right of everyone to access to optimal healthcare. Again, it should be clear that this argument applies just as much to the elderly as it does to anyone else.

Reasons have now been outlined why physical and mental health are basic human needs, why the same can be said for optimal healthcare and why everyone – irrespective of age – should be regarded as having an equal right to healthcare based on their need for it.

It follows from these reasons that everyone – again irrespective of age – has an equal need for and right to appropriate medical research.

Without such research, the continued success of healthcare can hardly be optimal – delivering the best results for the specific needs of individuals and populations. It also follows that an injustice will occur if the organisation and funding of medical research does not ensure that the available sources are shared equitably between all existing and morally similar categories of need. The injustice derives from the equality of the need for, and right to, optimal healthcare, again irrespective of age. Certainly, in a healthcare system such as the NHS, based on the principle of equal access to care linked to equal need, any organisation and funding of research which ignores this principle must itself been deemed unjust.

Other contributions to the Age-Net/MRC HSRC Workshop underlined the degree to which current medical research is prejudicial in its impact on the potential for benefit and harm among the elderly. It is the responsibility of others to outline the reasons why this is so and what is required practically for the conduct of medical research not to perpetuate injustice of the type outlined. One thing is clear. If the elderly controlled the organisation and finance of research and used their power to focus it only on their own health needs, a moral foul would be rightly called. For the same reason, an injustice is now being perpetuated against the old as regards the conduct of medical research.

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Jackie Brown. The health economist's perspective

It is generally recognised that resources are scarce and choices have to be made in the provision of healthcare.[1,2] Economics is principally about allocating resources efficiently. Efficiency is not about cost cutting, but about making choices that derive the maximum total benefit from the finite resources available. In the same way as evidence-based medicine stresses the need to use the best available formal evidence on effectiveness, health economics emphasises the need to assess formally the implications of choices over the deployment of resources. A number of economic evaluation techniques have been developed to aid this formal assessment and are increasingly being used to augment clinical evaluation.[3,4] Funding agencies such as the UK Medical Research Council now expect an economic evaluation to have been explicitly considered in proposed clinical trials.

Economic evaluation is concerned with the systematic comparison of both the resource use

consequences (costs) and the non-resource use consequences (outcomes) of alternative courses of action.[2,5] These might be, for example, alternative means of treating or managing a disease such as cancer or cardiac failure or alternative locations of care such as hospice versus home care. Given that there usually exists some kind of practice with regard to care, even if it is not to treat, it is the difference in costs and outcomes of the alternatives, including current practice, that is of interest. Economic evaluation thus takes an incremental approach. Results are presented as the difference in cost of the resources used, between the alternatives under consideration, compared with the difference in outcomes. The costs of the resources used, such as land, labour, capital and consumable items, are measured in monetary terms. The outcomes are mainly health consequences and how they are measured classifies the type of economic evaluation.[2,5] For example, a cost-effectiveness analysis measures the outcomes or effects in terms of natural units such as cases detected or life-years gained. A cost–utility analysis measures the outcomes in terms of utility, usually quality-adjusted life-years gained, whereby quality of life weights are assigned to the life-years gained.

Excluding older people from clinical trials, which form a framework for collecting data on costs and effectiveness, may have several implications in terms of being able to assess the cost-effectiveness of the treatments under evaluation. Compared with younger people, some older people may incur increased costs in terms of the healthcare and social services they receive and costs they incur themselves. The cause of the increased costs is likely to be related to the fact they experience increased co-morbidity[6] and therefore require longer inpatient stay, more outpatient visits, community care and hospital transport, for example. As mentioned previously, however, it is the difference in costs between the treatment options being evaluated that is of interest. Although the costs incurred by treating older people are likely to be greater than those for younger people, it is unclear how or whether the difference in costs between the treatment options will differ for older compared with younger people. The inclusion of productivity loss as a cost is controversial as it raises issues of double counting the outcomes or benefits, as well as issues of equity.[7,8,9] Where a new intervention has an impact on productivity loss, however, it is going to be less marked for older than for younger people, as older people are less likely to be economically active.

In terms of effectiveness, a new intervention may have fewer advantages for older people as they have a shorter life expectancy and may experience more co-morbidity and so may be less responsive to treatment.[6]

Excluding older people from clinical trials may reduce the generalisability of the findings. Including them may, however, distort the evidence for younger people. Including older people may also present practical problems. There may be difficulties associated with data collection. Poorer eye sight or reduced cognitive skills, for example, may affect patients' ability to fill in questionnaires relating to both health outcome and resource use or their ability to respond to interviews, for example to collect information on utility values (quality of life weights).

The solution may be separate trials for older people, but if a new intervention is only found to be cost-effective for younger people, it raises issues of equity and decision-makers could be accused of rationing by ageism. It may be that society is prepared to trade efficiency for equity, but the criteria for decision-making need to be made explicit. Studies have shown that many people in fact believe preference should be given to the young.[10]

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Mike Clarke. Should older people be included in clinical trials? The trialist's perspective: some personal thoughts

There is no simple answer to whether older people should be included in a randomised trial. It depends on the question that the trial is designed to answer. Everyone involved in the design of a trial should balance the advantages and disadvantages of including older people. Advantages might include increased generalisability for the results of the trial, higher incidence of the outcomes of interest (and thereby greater statistical power) and a population that is less likely to be transient. Possible disadvantages are that older people may be of such high risk of the outcomes of interest that the treatments will be ineffectual, of high risk of competing outcomes, less likely to take – or tolerate – the treatment and less available for outcome assessment. However, just as caution is needed if surrogate outcomes are used when analysing a trial, caution must also be applied if surrogate criteria are used in setting the eligibility criteria. If a trialist wishes to exclude patients who are frail, they should also use frailty as an exclusion criterion and not try to rely on an upper age limit as a surrogate for this.

Unfortunately, many trials have used an age threshold as an eligibility criterion. This has led to trials with age distributions that are very different from those of the patient population that would otherwise have been eligible.[1–3] As an example, almost half of the women diagnosed with breast cancer are >70 years of age, but <10% of the women who have taken part in randomised trials of adjuvant therapies for this disease were in this age group.[4,5] This is usually because an upper age limit had been set for entry into the trials and this may have been set simply as a matter of routine. It would be preferable if the norm could become that an upper age limit is not used. Instead, if a person met the other eligibility criteria for a trial, including uncertainty as to the treatment that would be better for them, he/she should be offered participation regardless of their age.

The exclusion of older people from a randomised trial may be determined in several ways, and these can impact unfavourably on the patient, others like them and those involved in the conduct of the research:

- It denies the person the right to take part in research that might increase the quality of their care.
- It decreases the generalisability of the trial's results of a trial to older people, including the person themselves as well as others like them.
- It reduces the number of people to whom participation in the trial can be offered, prolongs the accrual period for the trial, and thereby delays the production of a reliable answer.

From the perspective of the older person, there is growing evidence that patients who take part in randomised trials fare better than those who are similar but do not participate.[6] Therefore, if the best care available would come from participation in a trial, older people should not be denied this simply because of a purely arbitrary age threshold set when the trial was designed. In addition, if there is uncertainty between treatments, the most appropriate and ethical way to resolve this would be to use a random process to choose the treatment.

One of the most important advantages of including older people in trials is that it can be easier to generalise the eventual results of the study. If the condition under investigation is particularly common among older people or there is good reason to believe that their response to the treatments under investigation will be different to that of younger people, the trial must be designed to include them. Otherwise, there is a strong possibility that the results of the trial will either not be applicable to older people or will not be thought to be applicable.

Either way, the trial will have little or no influence on the care of patients in the future and will have failed in what is the principal aim of most medical research.

For the trialist, the decision on using age as an eligibility criterion should be guided by whether the inclusion of older people will help or hinder

the trial's ability to answer the question it is designed to address. In addition, their decision should also reflect the goal that all people, regardless of age, should have the right to be offered the opportunity to participate in a randomised trial, if there is uncertainty about which treatment is more appropriate for them.

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Max Bachman. Why older people should be excluded from trials

Reasons for excluding older people from trials can be divided into 'absolute' (or ethical and logical) reasons and 'relative' (or pragmatic and logistical) reasons:

Ethical or logical reasons
- Allocation to either intervention or control arm of a trial is dangerous.
- There is no reasonable chance of benefit from the intervention, for example because of short life expectancy.
- It is impossible to identify enough older patients who meet the eligibility criteria.
- The outcome cannot be measured in older patients, or treatment benefits are masked by co-morbidity.
- At earlier stages of the research process there is uncertainty about potential risks and benefits in older patients.

Pragmatic or logistical reasons
- Older people are more likely to have co-morbid conditions. Exclusion of older patients therefore results in a more homogeneous study population, which increases the statistical power of the trial.
- Recruitment and follow-up of patients are more difficult, for example because of restricted mobility.
- Different follow-up rates between the different arms of the trial may bias results.

None of these justifications, however, is based on age itself – they are based on factors that tend to be associated with age. Hence there are no absolute reasons why older people should be excluded from trials on the basis of their age alone. In some circumstances, however, age is so strongly associated with the real risk factor that age is a justifiable exclusion criterion. For example, renal function is very closely associated with age, and therefore older age may be a reasonable exclusion criterion when exposing patients to nephrotoxic agents. Such examples are relatively rare.

The ethical or logical reasons listed above are dependent on empirical knowledge which is often inadequate for clear decisions. The inclusiveness of trial populations should depend on the stage of the research process and the potential for harm.

For interventions that are potentially harmful, during Phase II and Phase III trials it may be reasonable to restrict the age range of patients. If the results of earlier studies give no cause for concern about potential harm, then later and larger studies should be as inclusive as possible, so as to maximise their generalisability. It was suggested that one should distinguish between Phase III trials, with restricted inclusion criteria, and Phase IV trials, which should be much more inclusive.

To research reasons for and effects of exclusions from trials, the following groups of stakeholders should be consulted: drug and device liaising authorities, research ethics committees, drug companies, research funders, academic clinical investigators and clinical trial coordinators.
A combination of research methods should be used, including interviews, questionnaires and vignettes, to assess stakeholders' attitudes to trial exclusions in different contexts. It would be interesting to compare what members of organisations say they do and what they actually do, for example by comparing interview responses with reports and protocols of trials carried out by the respective organisation.

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Matthias Egger. Why, when and how older people should be included in trials

We discussed the following issues: (1) rationale for inclusion of older people; (2) implications for trial design, and (3) implications for trial reporting. Finally, we discussed questions that could be put to stakeholders in a later phase of the project (see Annexe, p. 129).

Rationale for inclusion of older people

Speakers in the morning session discussed a number of related reasons for including older people:

- *Utilisation*: Utilisation of health services and drugs increases with age. Those aged >65 years comprise about 14% of the population in industrialised countries, yet they consume nearly one-third of all drugs.[1] According to FDA guidelines, patients included in clinical trials should in general reflect the population that will receive the drug when it is marketed. If clinical trials were complying with this recommendation, more older people and more women than men would be participating in clinical trials.
- *Co-morbidity*: Older people frequently have multi-organ disease and reduced renal and liver function and receive multiple drugs. Responses to treatments may differ in this population, interactions between drugs may occur and adverse drug reactions may be more frequent and more severe.[2–4] On the other hand, beneficial effects may be greater in absolute terms when effective interventions are used in high-risk patients.[5,6]
- *Uncertainty principle*: Without adequate data from clinical trials, uncertainty about the benefits and risks of interventions in older people remains. Co-morbid conditions may, or may not, put older people at increased risk. Such risks are best investigated in the rigorous setting of a clinical trial.[7] A recent analysis of cancer trials found no difference between elderly and non-elderly patients in efficacy of chemotherapy, haematological toxicity, nausea and vomiting.[8]
- *Distributional justice/equity*: Older people have equal rights to healthcare and therefore should be granted equal rights to be included in medical research.

Implications for trial design

Depending on the question asked, the inclusion of older people may have important implications for trial design. In particular, if we are interested in differences in treatment responses and adverse effects across age groups, we need to specify subgroup analyses in advance and take these into account when calculating sample size. Unplanned subgroup analyses are prone to produce misleading results.[9,10] For example, the various trials of beta-blockade after MI yielded several subgroup findings with apparent clinical significance.[10] Treatment was said to be beneficial in patients <65 years old but harmful in older patients; or only beneficial in patients with anterior MI.

When examined in subsequent studies, or in a formal pooling project,[11] these findings received no support.[10] This is a general phenomenon.

It can be shown that if a treatment effect overall is statistically significant and the patients are divided at random into two similarly sized groups, then there is a one in three chance that the treatment effect will be large and statistically highly significant in one group but irrelevant and non-significant in the other.[12] This was nicely illustrated by the Second International Study of Infarct Survival (ISIS-2) Collaborative Group, who analysed a large trial of interventions in acute MI by astrological birth sign, with astonishing results: the effect of aspirin appeared to be ineffective in patients born under Gemini and Libra whereas there was a strikingly beneficial effect for patients born under all other astrological signs.[13] Which subgroup 'clearly' benefits from an intervention is therefore often a chance phenomenon, inundating the literature with contradictory findings from subgroup analyses and wrongly inducing clinicians to withhold treatments from some patients, including older patients.[14–16] In trials not designed to detect differences in efficacy across different age groups, the overall estimate is likely to be the best estimate for any age group.

Implications for trial reporting

The exclusion and selective participation of older people pose a serious threat to the applicability of clinical trials.[17] In order to allow informed assessments of the applicability of clinical trials to older people, ethnic minorities and women, we

need adequate information on exclusion criteria and the characteristics of enrolled patients. Unfortunately, even when these groups are included, the demographic information that is published is often inadequate.[18] For example, it is important to know the exact age, sex and the co-morbidities of older people who are included in clinical trials because trial participants are generally younger, fitter and predominantly male.[19] Older, frailer individuals and older women tend not to be recruited even if no age or sex restrictions are reported. Indeed, it is often difficult to know to what extent older people in such studies represent primarily robust 66-year-olds: the oldest age group is frequently simply described as '>65'.[1] Most trial reports provide no age information by sex.[18]

The reporting of age-related information from the trials that do include older people needs to be improved. The exclusion of age groups should be justified and discussed and detailed information given on the enrolment process and the characteristics of study participants. This could be achieved by implementing structured reporting of age-related information.[20]

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Annexe: possible questions to stakeholders:

Do you apply age-related exclusion criteria?

If yes:
- Under what circumstances?
- Is cost an issue?
- Are adverse effects an issue?
- Is the spectrum of disease an issue?
- Is consent an issue?
- Is compliance an issue?
- Is co-morbidity an issue?

When do you think it is important to include older people in trials?

When do you think it is important to exclude older people from trials?

Richard Lindley. What are the likely main reasons for exclusion?

Older people have been systematically excluded from clinical trials for decades. There is little scientific support for this. Qualitative differences in treatment effects for young versus old are exceptionally rare in medicine (e.g. a treatment effect rarely changes direction as people age). More commonly there are quantitative differences (e.g. treatment effects are still generally in the same direction but vary in magnitude). Older patients often have higher event rates and this can lead to similar or greater absolute benefits for older patients.[1] Unfortunately, there are multiple excuses for exclusion and hence there is no 'quick fix' to the problem: possible reasons to explain why older people have been excluded from RCTs include the following:

- tradition (e.g. age limit of 65 years)
- access (e.g. cardiologist sees only younger cardiac patients)
- practicality of follow-up
- commercial fears
- inappropriate eligibility criteria (e.g. exclusion of those on any medication)
- inappropriate outcome measures
- unglamorous trial subject (e.g. faecal incontinence)
- shortage of academic geriatricians
- consent issues (.e.g. interventions for dementia)
- ageism.

Traditionally there have always been (arbitrary) age limits for clinical trials, the upper age limit varying with the age of the discussant and the era. Many trials probably had an upper age limit because it was traditional to do so and few were brave enough to question this habit.

Commercial trials almost always have age limits and this may be due to commercial worries. Drug companies want cost-effective trials with the smallest number of subjects to achieve a result. If they can recruit patients most likely to benefit from their new treatment they will save money. Older people tend to have more co-morbidity and have a greater chance of dying (from a variety of different pathologies) and this tends to dilute real treatment effects. Commercial exclusion of the old is most clearly seen in cardiology, especially the statins trials. Most cholesterol-lowering trials have had an age limit of 75 years. So far there is no good evidence to exclude those over 75 years old, yet a new cholesterol-lowering trial (PROSPER) will be performed with an age limit of 82 years old![2] It is surprising that commercial companies have not realised that a successful treatment trial with no upper age limit could open up an enormous market.

A recent cardiac trial[3] showed that bisoprolol improved survival for those patients with heart failure. Despite heart failure being a disease of older people, this trial had an upper age limit of 80 years of age. The authors then stated: "In our trial the mean age of patients was 61 years, at least a decade younger than that of most patients seen in clinical practice … there is, therefore, inadequate information about the effects of treatment in older patients and more data in the very old are urgently needed." Commercial pressures may have led to an age limit in the CIBIS-ll trial but a glance at the list of collaborators suggests another hypothesis. Did these collaborators (mainly cardiologists) simply not see many old people in their clinics?

Inappropriate outcome measures can also exclude the old. If trial follow-up is too demanding (e.g. monthly clinic visits), this may deter the less mobile elderly. A treadmill test may be impossible for frailer patients but a reasonable outcome measure for younger cardiology patients.

Trials relying on simple mortality outcome measures may be too simplistic for the older population as disability and dementia become major factors influencing quality of life. Measures of disability and cognition are difficult but methodological research has shown that some simple measures of outcome can be very powerful predictors of disability and quality of life.[4] Despite the inappropriate age limit of the PROSPER trial, the trialists are to be commended for including appropriate measures of disability and cognition in addition to the usual outcomes of major vascular events.[2]

The current obsession of funding agencies to fund genetic and molecular medicine projects also discriminates against the old as most of the distressing conditions of old age are not due to genetic disorders but to a complex mix of environmental factors and random events over decades. The successful treatment of these

conditions (e.g. faecal incontinence, osteoporosis, stroke) is likely to be a mixture of better service delivery (HSR) and better treatment of acute illness (randomised controlled treatment trials). Pragmatic trials of stroke units with appropriate meta-analysis have led to the widespread introduction of stroke rehabilitation units. The methodological research has saved more lives than all of the newer treatments for acute stroke put together.[5] The shortage of academic geriatricians compounds the problem of shortage of appropriate research funding.

Worries about consent for RCTs can also deter researchers including older people in trials. This is particularly important for trials of interventions for dementia. The solution probably includes greater awareness of the importance of trials within key consumer groups. Consumer involvement can lead to better trial design, better consent procedures and hopefully better support from consumer groups.[6]

The final reason for exclusion we have kept until last. After we have exhausted all the above reasons, we must admit that simply ageism may be the problem. Ageism is not simply a problem for the medical profession but, ask any geriatrician, and they will tell you that older people have a very low expectation of medical care. "Why bother with an old woman like me?" is heard too often on ward rounds and in the clinic.

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Ethnicity and health

MRC Head Office, London
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Main Speakers and Topics

Prof. Paul Dieppe **MRC HSRC** **Prof. Lesley Doyal** **School for Policy Studies, University of Bristol**	*Foreword*
Dr James Nazroo **Department of Epidemiology and Public Health, University College, London**	*Introduction: understanding race, ethnicity and health*
Prof. Raj Bhopal **Department of Community Health Sciences, University of Edinburgh**	*Exclusion and inclusion of ethnic minority groups in cardiovascular cohort studies*
Dr Seeromanie Harding **Social and Public Health Sciences Unit, MRC, London**	*DASH – Determinants of Adolescent Social well-being and Health – a school-based survey of multi-ethnic populations*
Ms Mahvash Hussain-Gambles **Centre for Research in Primary Care, University of Leeds**	*British South Asian underrepresentation in clinical trials*
Dr Colin Fischbacher **Department of Community Health Sciences, University of Edinburgh**	*Exclusion of ethnic minority groups from routine health statistics: repairing the gap in Scotland*
Dr Gabriel Scally **Public Health, NHS South West, Bristol**	*Britain's largest ethnic minority?*

Paul Dieppe and Lesley Doyal. Introduction to the 'Ethnicity and Health' workshop

Summary

The 'MEXICO' project, 'The Causes and Effects of Socio-Demographic Exclusions from Clinical Trials', has been commissioned by the UK Centre for Health Technology Assessment. Today's workshop is being held to help provide background to this project and to facilitate a sharing of perspectives and ideas amongst participants.

MEXICO is an investigation into whether women, older people and ethnic minorities are routinely excluded from (or inadequately represented in) clinical trials and whether this affects the external validity of the trial results. MEXICO is focusing on two exemplar drugs, statins for lowering blood cholesterol and preventing heart disease, and NSAIDs for musculoskeletal pain. The objectives are: to assess representation of women, older people and ethnic minorities in relevant trials, to compare this with the proportions in the population who are in potential need of the respective drugs and then, in turn, with the proportions in the population who tend to have the drugs prescribed for them.

The MEXICO collaborators are ascertaining whether the representation levels in trials result in an overestimation of the therapeutic effectiveness of statins and an underestimation of the toxicity of NSAIDs. 'Real world' epidemiological data are being extracted from health surveys and the MEMO pharmaco-surveillance system in Scotland. Qualitative work is also under way, in which the literature is being reviewed by Lesley Doyal, as part of a 'scoping' study examining the different social and legal contexts of trials in the UK and the USA.

Previous workshops have dealt with age issues and gender issues.

The collaborators have confirmed that statins trials (for secondary prevention) tend to focus on men and to exclude people over 75 years old. Ethnicity issues, moreover, rarely feature in statins trials. USA trials are generally more inclusive, however. In the 'real world', middle-aged people are more likely to be prescribed statins than older people. Statins seem to bring benefits for men and women and people of all ages, however.

NSAIDs trials tend to be small and brief. Women are well represented, but the ethnicity dimension hardly features at all. Trial participants may have been slightly younger than the 'real world' population who would use analgesics. Trials report GI adverse effects, but renal toxic events are rarely reported. This is not surprising because patients at renal risk have been excluded from the trials. Unlike the trials, 'real world' data suggest that frequency of toxic effects of NSAIDs are strongly associated with sex and age.

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James Nazroo. Understanding race, ethnicity and health

Summary

'Race' has become a redundant concept in social science. The social construct of 'ethnicity' has proved more useful but, as the classification used in the 2001 Census shows, the construct is still a complex, many-sided one and categorisation of ethnic groups tends to vary between different studies. Health Survey for England data show that the health status of most ethnic groups tends to be worse than that of the 'white English'. The rate of only fair or poor health increases with age in the population and this is also so in ethnic minority groups, resulting in very high levels of poor health in some groups in later life.

Different paradigms have been used in research into ethnicity and health. There is much evidence to support the notion of ethnicity as a structural aspect of society, particularly from the perspective of socio-economic disadvantage. Ethnicity is clearly associated with socio-economic disadvantage in terms of place of residence, overcrowding, economic status and household income. Socio-economic factors are closely associated with poorer health status within ethnic groups. In addition, ethnic minorities face problems of racial discrimination and harassment. These experiences may also be an influence on health status.

The definitions of ethnicity of Solomos and colleagues[1,2] and Fenton are worth considering. Ethnicity can also be conceived of as 'identity', and thus subject to many different influences. This should be borne in mind by empirical health researchers. For example, amongst South Asians smoking status appears to be simultaneously associated with family origin (Indian, Pakistani, Bangladeshi), with migration status, with gender and with social class. Ethnicity should not be viewed apart from other important health determinants. Brunner and colleagues[3] have suggested a model of the network of the factors (social, psychological, cultural and so on), which may influence health.

Ethnic groups should be appropriately represented in clinical trials. This should be done to ensure that the diversity of people's experiences and reactions are captured, to make sure the intervention is tried out in representatives of the types of populations who will use it in practice, to further understanding of inter-ethnic differences and similarities, and to put the new intervention to a more rigorous test.

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Raj Bhopal and Meghna Ranganathan. Exclusion and inclusion of non-white racial and ethnic minority groups in 61 key North American and European cardiovascular cohort studies

Summary

CVD disease is the most common cause of death in industrialised societies and is prevalent in all racial/ethnic groups in the USA and Europe. Some South Asian groups in the UK may have relatively high rates of CVD compared with other parts of the UK population. There are therefore sound reasons of epidemiology and equity why minority groups should be appropriately represented in CVD cohort studies. The present investigators assessed inclusion levels of ethnic minorities in a set of cohort studies relating to CVD, recording how the authors dealt with issues of ethnicity in their study design and reporting.

After a search of electronic bibliographic databases and registers, web searching and hand-searching of journals, 61 CVD cohort studies in English were identified. Most of these had been formally published. In all, 27 studies had been conducted in the USA and 34 in Europe. USA cohort studies tended to show slightly greater awareness of ethnicity issues. For example, 25 European studies did not report or discuss their study findings with reference to ethnic or racial groups, whereas only seven USA cohort studies failed to do so. Five USA studies focused on a specific minority group, whereas there were no European studies that did this. Overall, investigation of variations in health by ethnicity tended to produce 'black compared with white' results, and multi-ethnic comparisons, (which would represent ethnic diversity more accurately) have not been reported.

A number of design features contributed to low representation or lack of analysis of ethnic minorities, such as inadequate sample size or recruitment from non-inner-city populations, although exclusion of minorities was sometimes performed explicitly. The studies were prone to ethnocentricity, the tendency to perceive issues solely from the perspective of one's own culture. Relevant epidemiological data are required for ethnic minorities if appropriate health policies and services are to be developed for them. A 'needs-based' approach rather than a 'laissez-faire' approach should be adopted in research, with more CVD studies involving ethnic minority populations, especially in Europe, being performed.

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Seeromanie Harding. DASH: determinants of adult social well-being and health

Summary

The health differences between ethnic minority groups and the rest of the UK population are now well documented, but the cause of these differences (ethnic minorities commonly experiencing a relatively poor health status) is still a matter of intense debate. Socio-economic disadvantage contributes to these disparities but does not account for all of it.[1–5] Early growth is an important determinant of chronic diseases in later life[6] and there is increasing research interest in whether this plays a role in explaining ethnic differences in chronic disease in later life. The findings of migration studies, however, argue against an interpretation based on genomic variation. In a study of people of West African ancestry in Cameroon, Jamaica and Britain (Manchester), the prevalence of diabetes and hypertension was lowest in rural Cameroon and highest in Manchester.[7] These studies suggest that behavioural factors play an important role in ethnic differences in chronic disease. There are a substantial number of British-born children of migrants living in Britain but little is known about the intergenerational transmission of health risks.[8] Studies of Irish people living in England and Wales show that excess mortality (relative to the national average) persists across generations in spite of upward intergenerational social mobility.[9] Whether this trend will be different for other ethnic minority groups is yet to be established. Preliminary data suggest that the mortality of UK-born Pakistanis might be higher than that of foreign-born Pakistanis.[10]

The DASH (Determinants in Adolescent Social well-being and Health) Study is an MRC school-based study of children from different ethnic backgrounds living in London. It investigates the interplay between social factors – family life, deprivation, school life and psycho-social stress – and a range of health measures. The sample size is about 7000 students aged 11–13 years from 51 schools in London. The students complete a

questionnaire on social, health and behavioural factors and have a suite of medical measurements. Parents also complete a questionnaire. This study should provide a basis for determining whether adverse effects in adolescence can provide early indicators of chronic disease in later life.

At the time of this presentation, a pilot study had been completed and fieldwork was in progress. Some of the self-reported ethnicities of the children have been very surprising to the researchers. The long-term aim is to follow up the pupils after 2 years to investigate changes in health-related behaviour and health status at age 13–14 years among children who had baseline measures aged 11–12 years, and how these changes may interact with social, economic and biological factors to influence differential development of health risks among ethnic groups. More details of the study can be found on the DASH website at http://www.msoc-mrc.gla.ac.uk/DASH/DASH-MAIN.html.

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Mahvash Hussain-Gambles. Involving South Asian people in clinical trials

Summary

This is a preliminary report of a research project investigating the involvement in clinical trials of South Asian people in the UK. A literature review was undertaken, a selection of trial reports was analysed and qualitative research consisting of interviews with 25 health professionals was carried out. Interviews with South Asian lay people and trial participants have also taken place and will be reported in the near future.

The literature indicates that people from ethnic minorities are frequently underrepresented in clinical trials, especially in the UK. In addition to being inequitable, this may compromise the generalisability of the trials. Analysis of six trials with Yorkshire/Humber Region involvement confirmed that representation of South Asian people was much lower than their actual proportion (3.8%) in the population of Great Britain. The situation has greatly improved in the USA, probably owing to the National Institute of Health Guidelines of 1993, but only after some notorious episodes such as the 'Tuskagee Experiment' in which black American participants were deliberately put at risk.[1]

In the literature, we identified significant barriers to inclusion of ethnic minorities, such as trials being carried out in areas with a small proportion of ethnic minorities and unwillingness or inability of trialists to make allowances for cultural differences or language difficulties.[2,3] Furthermore, our original research revealed that health professionals are often unaware of the problem of underrepresentation in trials or are impeded by their unfamiliarity with ethnic cultures and by lack of culturally appropriate tools. Health professionals tend to adhere to some stereotypes concerning South Asians and trial situations, such as that South Asians will be non-compliant, and

that South Asian women do not make their own decisions and have high levels of 'modesty'.

We propose a set of strategies for remedying the situation, strategies aimed at healthcare provider level, at community level and at individual level. Such strategies include training for health professionals to expand their knowledge of equality issues and ethnic culture and, to complement this, education of ethnic minority patients and appropriate support for them in considering or participating in clinical research.[4] We strongly advocate, as a practical step forward, the development and evaluation of a teaching/training package for clinical trial recruiters.

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Colin Fischbacher. Exclusion of ethnic minority groups from routine statistics: repairing the gap in Scotland

Summary

The reduction of inequalities in health is a priority in Scotland. Policy and action plans for promotion of health in ethnic minorities are enshrined in various Scottish Executive documents (such as 'Towards a Healthier Scotland', 1999). Good-quality data are essential for establishing the extent of health inequalities and for monitoring the effect of programmes promoting health gain.

However, as in other parts of the UK, a number of definite 'information gaps' are evident. In the Scottish setting, the shortfalls include small numbers from ethnic minorities in national health surveys, infrequent recording of ethnicity in hospital episode statistics and little ethnicity-related data in primary care systems. Various health-care databases in Scotland collect ethnicity data but the records tend to be incomplete and do not match up directly with census categories of ethnicity. There is a need for a routine system, spanning Scotland, for collecting health information according to ethnicity, based on a single, universally accepted protocol, supported by appropriate funding and by trained staff. Discussions are under way to see if such a comprehensive system, a radical option, can be achieved.

Such a major project will take time to design and implement. In the interim, a number of pragmatic solutions could be tested out, such as analysis of mortality by country of birth of parents (as held in the Scottish birth record), imputation of data from England and Wales Health Surveys and the use of algorithms which search for South Asian names in existing databases. The routine recording of ethnicity on birth and death certificates might be helpful. Some degree of data linkage might be possible between mortality records and hospital discharge data. These methods all have drawbacks, and in particular do not involve a self-assignment of ethnic label by the people concerned themselves. The short-term solutions are imperfect but an iterative approach is probably warranted, with different steps being taken before the creation of a comprehensive system.

Gabriel Scally. Britain's largest ethnic minority?

Summary

Results from the 2001 census reveal that 1.2% of the England and Wales population are 'white Irish', but the percentage is somewhat higher in some London boroughs. A number of important health indicators such as smoking and body mass index are worse in this group than in the 'white English'. In the past, poorer Irish people migrated to Great Britain in search of manual work and suffered some of the worst health problems in nineteenth century Britain. Many 'travellers' in contemporary Britain would describe themselves as Irish and in terms of lifestyle are clearly a distinct group, but these people are only a small part of the Irish community in Britain. The UK Commission for Racial Equality is of the opinion that the difficulties of Irish people in Britain have not been generally recognised.

A number of pieces of research indicate comparatively poor health in present-day Irish emigrants and their families. For example, Harding and Balarajan's analysis of mortality in emigrants to the third generation[1] shows that

excess mortality in Irish families in England and Wales has actually increased in succeeding generations. A comparison of survey data from England and Wales, Northern Ireland and the Irish Republic[2–4] also suggests that some health-related behaviours may be, on average, worse in Irish emigrants than in their peers in the island of Ireland.

It is not clear why these health indicators are unfavourable. The effect could be due to social exclusion, socio-economic disadvantage or selective migration. It is conceivably artefactual, people with an Irish background who also have health or social disadvantage being more likely to label themselves as Irish. As evidenced by members of the Irish national football team, definitions of Irish identity may vary greatly according to context. These explanations are not mutually exclusive. In terms of research into health promotion, the Irish should be recognised as an ethnic group within Britain.

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Ethnicity and health: summary of workshop discussion chaired by Lesley Doyal

In this summary, where a specific presentation was a point of reference in the discussion, the presenter's surname is given in italics.

'Equity and justice' versus 'protectionism'

Paul Dieppe's MEXICO project team have examined sets of clinical trial reports for two commonly prescribed drugs. However, ethnicity as a participant variable is seldom reported or addressed by the trialists (*Dieppe*). There is clearly a need for more consideration of the issue of 'justice' in the representation of ethnic groups in clinical trials and in health research in general (*Bhopal*, *Hussain-Gambles*). If members of ethnic groups are likely to receive the new treatments in practice, then it is equitable and just (as well as scientifically appropriate) for those ethnic groups to be appropriately represented in trials (*Nazroo*). By the same token, ethnic groups should also be appropriately represented in longitudinal and aetiological studies, for it cannot be assumed that the factors under study will influence the health of members of different ethnic groups in an identical way (*Bhopal*).

It might also be considered a duty for people from all sectors of the population to contribute to health research by means of participation and a right for them to have access to new treatments through trials and to understand this important aspect of community health. The move towards justice is a move away from 'protectionism', the exclusion of population subgroups from research, motivated by the desire to avoid harming them (and to avoid harming the reputation of the researcher). A degree of protectionism for appropriate reasons is, of course, highly ethical. The outstanding problem is one of finding a balance between justice and protectionism. Similar problems are encountered in the sphere of routine health statistics (*Fischbacher*); coverage of ethnic groups (as distinct entities) is not good but improvement of the situation may entail the encroachment of researchers on confidential social data.

'Science' versus 'equity and justice'

The CONSORT statement, the widely adopted guideline for the reporting of trials, does not include any stipulation for the reporting of the ethnic make-up of a trial sample. It might be argued that a well-designed therapy will be effective regardless of the ethnic group being treated. This is a problematic position to take where psycho-social and behavioural therapies are concerned, as the latter interventions may be greatly influenced by culture and language. Some scientists would claim to be on more solid ground with drug treatments, maintaining that drugs will have equivalent therapeutic effects irrespective of the ethnic group being treated. This is by no means firmly established. Different population groups metabolise certain drugs differently, to some degree at least (*Bhopal*). Little systematic work has been done to determine the magnitude of this differential effect (or set of effects) and whether it has any practical ramifications for the effectiveness and prescribing of drugs. The issue must therefore be regarded as remaining open.

'Practicability' versus 'equity and justice'

If ethnicity is to be a category of analysis then sample sizes in studies will have to be increased to produce adequately powered studies with sufficiently precise results for this category. The problem will of course be multiplied if one wants to discriminate statistically between a number of different ethnic groups. If one is also concerned about treatment effectiveness according to age and sex, then the sample size will have to be increased still further. This is a weighty practical problem, which is in considerable tension with notions of justice. Equitable health research could become so large (in terms of numbers of participants needed) and so unwieldy (in terms of recruitment procedures) and hence so expensive that fewer treatments could be tested out. Ethnic minorities (and indeed the whole population) might suffer overall as a result.

'Barriers to inclusion' versus 'equity and justice'

It is probable that some researchers regard the inclusion of ethnic minorities in research as inherently problematic, believing that such people may have linguistic and cultural difficulties in participating (*Hussain-Gambles*). Although this might sometimes be true, in many cases this will be an incorrect assumption. On the other hand, people from ethnic minorities might refuse to participate in health research, being wary of or lacking understanding of the aims and methods of research. Such 'educational' problems in the researchers and the research participants might be overcome by policy change and the use of educational methods. A suitable training package remains to be developed in the UK, however. In the USA there has been the political will to legislate and take political action to promote fair representation of ethnic groups in trials. This process has not yet happened in the UK and there are not yet any signs of it happening.

'Ethnicity' as an interactive, dynamic variable

A number of presenters (in particular *Harding*, *Scally*) observed that definitions of ethnic group varied amongst researchers, and between contexts. 'Ethnicity' ultimately depends on how an individual views her or himself, and this might be in contradiction to how a researcher regards their ethnicity (*Nazroo*). As a research variable ethnicity is not isolated from other factors and probably interacts with age, gender and social class. The process of ageing might take different forms in different ethnic groups. Social class differences within ethnic groups might change over time. Health status might be viewed differently by different ethnic groups, although the available evidence was conflicting here. Definitions of ethnicity might even have different significance according to the research context (e.g. trial, cohort study, case–control study).

Closing considerations

It is a desirable goal for people from different ethnic groups to have equitable rights and ability to participate in health research. However, if research with appropriate participation by ethnic groups is to be well designed and appropriately analysed and interpreted, much methodological work still needs to be done. The next step should be for existing methodological knowledge to be gathered and reviewed, with lacunae being identified. In particular, problems in classification need to be addressed, and interventions for optimising ethnic participation need to be developed. The workshop closed with these challenges in mind.

Gender exclusions from health care research

MRC Head Office, London
February 2002

Main Speakers and Topics

Prof. Lesley Doyal **School for Policy Studies, University of Bristol**	*Introduction to gender and healthcare research*
Dr Sarah Payne **School for Policy Studies, University of Bristol**	*Gender and irritable bowel syndrome; a case study*
Dr Judith Fuchs **Berlin Centre of Public Health,** **Technical University of Berlin**	*Gender analysis in public health: a German example*
Dr Kate Hunt **MRC Social and Public Health Sciences Unit, Glasgow**	*Gender in non-communicable diseases research*
Dr Rosalind Raine **London School of Hygiene and Tropical Medicine**	*Does gender bias exist in the use of specialist health care?*
Prof. Janet Darbyshire **MRC Clinical Trials Unit, London**	*Does sex matter if you randomise?*

Lesley Doyal. Introduction to gender bias and health research

Summary

Debates about sex/gender bias in health research have varied across national settings. The USA and Canada, for example, have different approaches. In the UK these issues have so far received little attention. It is important to distinguish between the terms 'sex' and 'gender' when bias is being considered. It is also important to investigate how different types of bias might manifest itself in different branches of health-related research. It is also clear that age and ethnicity issues interact with sex/gender and researchers must take this into account. More work is needed to clarify the nature of sex/gender, age and ethnicity as variables within the research setting.

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Workshop discussion on introduction

International context

The international dimension to the issue of gender bias in health research is one that must be recognised and is worthy of further investigation. The USA is of particular interest, because 'equity' in clinical trials has received legislative backing, in particular through the NIH Revitalization Act of 1993. It is not clear why the notion of social fairness with regard to inclusion of people of different backgrounds in trials has received such comparatively strong support in the USA. It may be that there is greater mobilisation of interest groups there, spurred on by the obvious inequities in the delivery of healthcare. For some groups, for example, people in need of treatment for HIV, involvement in trials may be seen as a way of gaining access to expensive medicines. Conversely, people in the UK may assume that the existence of the NHS means that equity in trials is somehow safeguarded. However, the question might not have occurred to them in the first place. It is also possible that the concept of equity differs between countries.

Differences in the terms 'sex' and 'gender'

It is important in health research to distinguish between biological differences between males and females (sex) and differences in social roles and socially constructed characteristics (gender). Ignoring the distinction can lead to misunderstanding of the significance of research findings on the part of both researcher and researcher-user.

Sex/gender in different area of health research

The inclusion of women in health research is an important issue, yet the problem is likely to be a different one according to the type of study being undertaken. Would the same type of gender bias be present in an observational study as in a clinical trial? Would the same type of gender bias be present in the trial of a drug as in the trial of a form of health service delivery?

Interaction between sex, gender, age and ethnicity

Sex/gender, age and ethnicity are all important factors that should be taken into account in health research, but it is conceivable that they interact, and in different ways according to the area of health being studied. The notion of interaction is very important, even though it is likely to cause many methodological problems for researchers. The most salient example is making sure that sufficient numbers of people with different combinations of these characteristics are represented in health research. This would, in theory, necessitate an expansion of sample sizes and so also of research costs. This is a problem for the qualitative as much as the quantitative researcher.

Further considerations

The design of a study that appears, at a general level, to be inclusive of people from different backgrounds could still entail exclusions indirectly. For example, certain exclusion criteria, relating to access to a study centre in a trial, might screen out people with certain social characteristics. The design of a trial protocol, particularly if it entailed many clinic visits or a time-consuming regimen, might be a barrier to giving consent for some groups. It might also be noted that an efficacy trial of a drug (studying if and how the drug has a therapeutic effect under optimum conditions) may suffer from lack of external validity, that is, generalisation to health service use, but this should not necessarily be described as a bias issue. Effectiveness studies (studying if an intervention has the desired effect in a real-world setting under less than optimum conditions), on the other hand, can justifiably be criticised on bias grounds if certain social groups are not adequately represented in the sample.

Sarah Payne. Gender and irritable bowel syndrome: a case study

Summary

Irritable bowel syndrome (IBS) is presented here as a case study in sex/gender issues in health research, revealing different ways in which sex/gender issues might manifest themselves in health-related research. Sex/gender issues arise in the health-seeking behaviour of people with IBS, consultation rates, possible biological and hormonal causes, diagnostic criteria and end-points in trials. Issues of personal history and psychological well-being are prominent in IBS. Gender dimensions might be important in such psycho-social issues but are rarely explored.

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Workshop discussion on gender and irritable bowel syndrome

IBS is an interesting exemplar (at least for researchers) because of the complex way in which gender may affect its natural history, symptoms, clinical perception and treatment. Gender bias might even be present when the results of laboratory tests for IBS patients are being considered. IBS might be a condition in which different trial end-points for men and women should be considered. Symptoms of anxiety and depression are also associated with the syndrome. Trials in IBS treatments can have perplexing results, the placebo sometimes having a better outcome than the experimental treatment. It is possible that the placebo effect itself has a gender dimension. However, a placebo effect should not be divorced from a 'context' effect. 'Trial physicians' might have a greater non-specific therapeutic effect than physicians in routine practice, perhaps having more time to spend with patients and enabling patients to be more open about their problem and to have more confidence in the intervention being offered.

Judith Fuchs. Gender analysis in public health. Results of a survey and a review of literature: a German example

Summary

Major problems of gender bias are apparent in the German public health research community. The latter can be summed up as androcentricity gender insensitivity and double standards. After a review of the theoretical and methodological literature was undertaken, leaders of public health projects in Germany were surveyed. Results from male and female researchers were analysed separately. Male researchers were more likely to ignore sex/gender issues in a number of elements of their research projects. A sample of research papers in German-language public health journals was also reviewed for their treatment of sex/gender issues. In most cases gender issues were not mentioned.

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Workshop discussion on gender analysis in public health

Respondents to the survey tended to support the notion of minimising gender bias, but it would have been strange if they had not agreed with something socially desirable presented to them in a survey questionnaire. The survey may have influenced practice but it is difficult to measure this. Likewise, the American legislation may have had an international influence. It is conceivable that research findings which do not reveal a gender difference remain unpublished or focus on a combined result for people of both sexes. Of course, publication may actually be facilitated by combining results for men and women to yield more statistically precise results. The problem can also be viewed as one that is probably the result of a long-standing mind-set in individual researchers and clinicians.

Kate Hunt. Gender in non-communicable diseases research

Summary

In 2000, WHO commissioned a review on gender and non-communicable disease. The research focus was narrowed to CHD and lung cancer, however. A literature search was undertaken for relevant papers from the period 1996 to 2000. Papers were then divided into five groups,

according to quintiles of differences in life expectancy between the sexes in the country studied. Most papers lacked a 'gender' focus, and few systematically addressed 'sex/gender' issues. Most evidence on epidemiology of gender and CHD and lung cancer is dominated by studies from limited parts of the globe, notably the USA. Although gender issues in these diseases may take different forms around the world, there is a notable lack of studies from the developing world.

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Workshop discussion on gender in NCD research

The WHO review of the gender issue in non-communicable disease research reveals an absence of gender focus around the world and a domination of research by a few countries, most notably the USA. Good examples of how ethnicity issues might interact with gender issues were uncovered during the review. For example, smoking in China was an important health problem in women, but the Western epidemiology of lung cancer might have little relevance in such a setting. We cannot assume that Western social processes will apply outside Western social settings. The ideal of 'global equity' in health research is surely one that is worth pursuing.

Rosalind Raine. Does gender bias exist in the use of specialist health care?

Summary

The international literature on the use of specialist services was critically appraised using quality criteria. The topic areas that emerged were coronary artery disease, renal transplantation, HIV/AIDS, mental illness and other procedures. There appeared to be gender differences in the management pathway to angiography, but no differences in subsequent revascularisation rates. Men were more likely to receive renal transplantation and the HIV drug AZT. Mental health services might be provided differently for men and women. It is not clear whether these differences exist due to real differences in need or to perceived differences in need or because of clinical prejudice. Primary research in this area is often methodologically limited.

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Workshop discussion on gender bias in specialist health care

This is another important sphere of gender-related research, but one that necessarily involves understanding complex pathways and making subtle interpretations. For example, gender bias or inequity must not be confused with differential treatment according to need; a clinician might seem to be unfair but might in fact be acting on his/her perception of the patient's need and of the likely outcome of treatment. Availability of resources might also be an added factor in this equation. A clinician might feel it is an ethical imperative to allocate resources where they will have maximum effect. On the other hand, it is possible that clinicians have mistaken or prejudiced perceptions of need and likely outcome. The nature of a disease might also complicate decision-making. For example, the incidence of joint replacement shows a differential according to gender, but it is improbable that this is due solely to a gender-related inequity or prejudice.

One possible research design to investigate this issue is that of the administration of vignettes to clinicians who record how they would react in the situation depicted in the vignette. A further development of this approach is to have actors present symptoms and behaviours to an unwitting clinician, who then reacts to these symptoms and behaviours. This might be done, for example, with ethnic actors presenting CHD symptoms. It is true that this involves some ethical problems but it is likely to be very revealing and have great benefits in the long term.

Janet Darbyshire. Gender exclusions in trials. Does sex matter if you are randomised?

Summary

Sex and gender differences are vital considerations

in health research, particularly because of the way biological differences might affect the course of a disease and the patient's response to treatment. Sex/gender might also interact with other extrinsic factors. Cell counts and viral load are useful markers in HIV treatment, but interpretation has to vary with the sex of the patient. If we are unsure about extrapolating from men to women (or vice versa), then we must consider increasing sample sizes (with gender stratification or separate trials) and also be prepared to increase or reallocate funding for trials commensurately.

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Workshop discussion on gender exclusion in trials

Clinical trials are frequently designed and reported without sufficient regard to sex and gender issues. This situation exists in spite of the different ways in which women might react to a drug or to the delivery of a package of healthcare. Avoidance of gender bias in research will necessitate more considered study designs, more careful consideration of the existing literature and knowledge base and probably greater costs due to larger numbers of women.

The recent paper by Lee and colleagues[2] indicates that representation of women in trials for coronary medication has improved since 1966 but only marginally, with 26.7% of trial participants being female in the period 1996–2000. RCTs are frequently extolled as the least biased and most highly evolved form of medical research. The following points may be taken as considerations which tend to qualify this status.

Participation/eligibility

- Protocol stipulations, such as availability, may make it more difficult for women than for men to take part.
- In some contexts it may be that women access specialist, secondary care services less frequently than men and so are less likely to be in the setting where most trials are conducted.
- It may be that in some circumstances there are gender issues in relation to the giving of consent.

Safety

- Since the thalidomide case, drug studies have tended to exclude women who could become pregnant during the trial process; this might be seen as a justifiable safety measure or a form of discrimination.
- It might be argued that some exclusions are due to regard for the protection of potentially vulnerable groups; however, this might also be seen as a means of screening out potential non-compliers.

Process measurement

- Other sex issues that might be relevant include physiological processes specific to women, such as menstruation, and their relationship with drug effectiveness and side-effects.

Outcome measurement

- Many outcome measures in frequent use have an element of gender bias, for example, measures of male-oriented functional tasks, which can result in apparent differences in severity of outcome between men and women; gender-specific outcome measures may need to be developed.

Interaction with other factors:

- Sex/gender issues are both confounded with age, ethnicity, social status and deprivation, making it impossible to deal with gender exclusions in isolation.

Appendix 2

UK and European guidance on inclusions in clinical trials/health and social research

Search of websites at February 2003 by Christopher Bartlett

Council for International Organizations of Medical Sciences (CIOMS)

http://www.cioms.ch

International ethical guidelines for biomedical research involving human subjects. 2003.

General guidelines for countries wanting to draw up their own regulations. Presumably no legislative force.

Guideline 16. Women as research subjects. Recommends that women of reproductive age make up their own minds on whether to participate and should not be excluded as a matter of course.

COREC (Central Office for Research Ethics Committees)

http://www.COREC.org.uk

There is nothing specific about inclusion of different groups in trials.

European Agency for the Evaluation of Medicinal Products (EMEA)

http://www.emea.eu.int

ICH Topic E6. Guideline for good clinical practice. Revised 2002. Harmonised principles, giving guidance to ethical committees within member countries. Personal communication: EMEA does not make detailed recommendations on inclusions.

UK MRC

http://www.mrc.ac.uk

MRC guidelines for good clinical practice in clinical trials. 1998.

Good research practice. 2000.

Detailed practical and ethical guidelines for MRC-sponsored trials. No policy on exclusions.

Association of the British Pharmaceutical Industry (ABPI)

http://www.abpi.org.uk

Code of practice for the pharmaceutical industry. 2001.

Nothing on exclusions here. There are model agreements/contracts for use with NHS bodies but largely dealing with the administration of research.

UK Medicines Control Agency (MCA)

http://www.mca.gov.uk

MLX287 consultation letter on the Medicines for Human Use (Clinical Trials) Regulations. 2003. Consultation on how an EC directive should be put into UK law (Directive 2001/20/EC 2001). This seems largely a move to have basic standards of clinical practice across the EU and no sign of exclusions material.

UK Department of Health

http://www.doh.gov.uk/research

Research governance framework for health and social care (in England).

This is more interesting. It is not clear how this should be interpreted and of course it covers social as well as health research, but it is potentially far-reaching.

Part 2: Ethics.
Para 2.2.7. "Research and those pursuing it should respect the diversity of human culture and conditions and take full account of ethnicity, gender, disability, age and sexual orientation in its design, undertaking and reporting. Researchers should take account of the multi-cultural nature of society. It is particularly important that the body of research evidence available to policy makers reflects the diversity of the population."

Para 2.7.2. Key elements of a quality research culture includes "Valuing the diversity within society". "Hard to reach groups such as the homeless" are mentioned.

Box B. "The organisation's research strategy values diversity in its patients or users and its staff and promotes their active participation in the development, undertaking and use of research."

Scotland, Wales, Northern Ireland

The equivalent documents for Scotland and Wales are substantially the same with some different emphases: Scottish version mentions avoidance of unnecessary discrimination. Welsh version mentions religious beliefs/non-belief and language as part of diversity. Welsh speakers (~20% of the population) have a legal right to have research conducted in Welsh. Northern Ireland version at consultation stage. Religion is not mentioned.

Cochrane Handbook

http://www.cochrane.dk/cochrane/handbook/hbook.htm

Reviewers looking at trials are advised to be aware of sex, age and cultural issues which may mean that the trials may have limited applicability to their review question. However, note that subgroup analysis is advised in the Handbook more or less as a last resort as the chances of finding a subgroup difference purely by chance (due to sampling error) are fairly high!

So really reviewers have to err on the side of the 'average overall effect', as the problem goes back to the raw material, the trials, which they cannot control.

National Collaboration for Ageing Research (MRC, ESRC, etc.)

http://www.shef.ac.uk/ukncar

This seems to be more about inter-disciplinary work than representation of older people in 'young people' research.

Appendix 3

Database search strategies for statins trials and for NSAIDs trials

Search for statins RCTs in Ovid MEDLINE

The electronic search for statins RCTS was conducted in Ovid MEDLINE in August 2001 and is an update of a previous search by Ebrahim and colleagues[1] extending to mid-1997.

1. RANDOMIZED CONTROLLED TRIAL.pt.
2. CONTROLLED CLINICAL TRIAL.pt.
3. RANDOMIZED CONTROLLED TRIALS.sh.
4. RANDOM ALLOCATION.sh.
5. DOUBLE BLIND METHOD.sh.
6. SINGLE-BLIND METHOD.sh.
7. or/1-6
8. (ANIMAL not HUMAN).sh.
9. 7 not 8
10. CLINICAL TRIAL.pt.
11. exp CLINICAL TRIALS/
12. (clin$ adj25 trial$).ti,ab.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
14. PLACEBOS.sh.
15. placebo$.ti,ab.
16. random$.ti,ab.
17. RESEARCH DESIGN.sh.
18. or/10-17
19. 18 not 8
20. 19 not 9
21. COMPARATIVE STUDY.sh.
22. exp EVALUATION STUDIES/
23. FOLLOW UP STUDIES.sh.
24. PROSPECTIVE STUDIES.sh.
25. (control$ or prospectiv$ or volunteer$).ti,ab.
26. or/21-25
27. 26 not 8
28. 27 not (9 or 20)
29. 9 or 20 or 28
30. statin$.tw.
31. simvastatin.tw.
32. pravastatin.tw.
33. lovastatin.tw.
34. fluvastatin.tw.
35. atorvastatin.tw.
36. cerivastatin.tw.
37. HMG$.tw.
38. co-reductase inhibitor$.tw.
39. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. 29 and 39
41. limit 40 to yr=1997-2001

Outline search for osteoarthritis trials in various databases

The electronic search for NSAIDs controlled trials was undertaken by Chard and colleagues,[2] as part of an investigation into osteoarthritis treatment, extending up to March 1998. Ovid MEDLINE, Ovid EMBASE, BIDS and the Cochrane Library were searched. An outline of elements common to all the electronic search strategies is given.

- 'Osteoarthritis' as keyword and/or MeSH heading search.

Combined with each of the following:

- 'Survey' and synonyms as keyword and/or MeSH heading search.
- 'Experiment' as keyword and/or MeSH heading search.
- 'Clinical trials' and synonyms as keyword and/or MeSH heading search.
- 'Review' as keyword and/or MeSH heading search.
- 'Management guidelines' and synonyms as keyword and/or MeSH heading search.

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Appendix 4

Statins papers scrutinised and excluded from the study (with reference numbers)

No usable outcomes (1 paper)

Chylack *et al*. (1993).[166] Study of lovastatin and cataracts, but no CVD or lipid outcomes.

Confounded, more than one additional drugs or no statins (8 papers)

Kane *et al.* (1990).[167] Various combinations of lipid-reducing drugs were used.

Tomei *et al.* (1993).[168] Simvastatin was compared with simvastatin with fish oil. Effects related to simvastatin were not clear.

Sacks *et al*. (1994).[169] Statins group was topped up with nicotinic acid, cholestyramine, and gemfibrozil.

Hunninghake (1998).[170] Factorial trial with all patients receiving statins.

Alaupovic *et al*. (1999).[171] Factorial trial with different dosages of lovastatin, chiolestyramine, warfarin and placebo. Effects related to statins were not clear.

Campeau *et al*. (1999).[172] Factorial trial with all patients receiving statins.

Arntz *et al*. (2000).[173] Statins group was topped up with cholestyramine and niacin.

Ito *et al*. (2001)[174] Two dosages of pravastatin were compared.

Not RCT (2 papers)

Kyushu Group (2000).[175] Trial was converted to an observational study.

Hosokawa *et al*.[176] (2000): Randomisation was not reported for this study.

Duration too short (8 papers)

Sprecher *et al*. (1994).[177] Follow-up was <6 months/26 weeks.

Civeira *et al*. (1999).[178] Follow-up was <6 months/26 weeks.

Ozerova *et al*. (2000).[179] Follow-up was <6 months/26 weeks.

Ose *et al*. (2000).[180] Follow-up was <6 months/26 weeks.

Blann *et al*. (2001).[181] Follow-up was <6 months/26 weeks.

Schwartz *et al.* (2001).[182] Follow-up was <6 months/26 weeks.

McPherson *et al*. (2001).[183] Follow-up was <6 months/26 weeks.

Appendix 5

NSAIDs: Cox-1 and Cox-2 inhibitors ('coxibs')

Our investigation of NSAID trials was restricted to the traditional, 'Cox-1' inhibitors. Over recent years a new class of NSAIDs, the 'Cox-2' inhibitors or 'coxibs' have been introduced. In this Appendix we offer a brief explanation of the differences between these two classes of NSAIDs, and our justification for limiting our study to the older types of NSAID.

Inflammation is one of the main drivers of symptoms in musculoskeletal disorders, so anti-inflammatory therapy has been a mainstay of symptomatic therapy for the last 50 years. Steroids are effective, but very toxic, particularly if used chronically, so NSAIDs became the treatment of choice. Following early use of aspirin, indomethacin was introduced in the 1960s, followed by ibuprofen and then a plethora of other 'me-too' agents. The justification for the licensing of several different drugs was based on individual variations in response and the search for an improvement in the balance of effectiveness and toxicity, driven by increasing awareness of the toxicity of NSAIDs, particularly to the GI mucosa.

In 1971, Vane showed that the mechanism of action of NSAIDs was through inhibition of the enzyme cyclooxygenase,[1] resulting in reduced synthesis of pro-inflammatory prostaglandins (prostaglandins also protect the GI mucosa and have important roles in renal, platelet and neuronal function). In the early 1990s, it was found that there were two isoforms of cyclooxygenase: Cox-1 and Cox-2.[2] It was initially suggested that whereas Cox-1 was constitutively expressed, Cox-2 was only expressed by inflammatory cells, so selective Cox-2 inhibition became a major new target for the pharmaceutical industry. The first two agents marketed as 'selective Cox-2 inhibitors' (now known as coxibs) were launched in late 1998 and 1999 (celecoxib and roficoxib, respectively). However, retrospective studies have shown that some of the agents launched earlier already possessed some selectivity, most notably meloxicam and nabumetone. Further confusion has now been added by findings that celecoxib is not in fact very selective,[3] and that Cox-2 is widely distributed in many normal body tissues.[4]

The coxibs (celecoxib, roficoxib and more recently valdecoxib and enterecoxib) have been tested in trials involving larger numbers of patients treated for longer periods than was the case for earlier NSAIDs.[5] This occurred partly because they have appeared more recently and partly because of the need to demonstrate superior toxicity profiles in comparison with the traditional NSAIDs. In addition, they have been considered to be of potential value in the treatment of different conditions, including intestinal polyps. Hence, their trial profiles are completely different from those of conventional NSAIDs. They have also been marketed extremely aggressively, and since 1999 have made a significant impact on prescribing habits and market shares of the different NSAIDs. The justification for this uptake, and their claims to improve safety, are now being challenged.[6,7] It is clear that their development has caused major changes in trial approaches and prescribing over the last 3 years.

Because of the fast movement of the field, the very different trial profile of 'coxibs' and insecurity about their final position in the pharmacopoeia, we elected to omit them from our investigation. Subsequently, after completion of the first draft of this report, new data indicate that 'coxibs' have cardiovascular toxicity. Rofecoxib has been withdrawn and the use of celecoxib limited. The future of the whole class is now in doubt. In retrospect, it would appear that we made a fortuitous decision for the purposes of this study.

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