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BMJ Open Heavier smoking may lead to a relative increase in waist circumference: evidence for a causal relationship from a Mendelian randomisation meta-analysis. The CARTA consortium

Richard W Morris,^{1,2} Amy E Taylor,^{3,4} Meg E Fluharty,^{3,4} Johan H Bjørngaard,^{5,6} Bjørn Olav Åsvold,^{5,7} Maiken Elvestad Gabrielsen,⁸ Archie Campbell,⁹ Riccardo Marioni,^{9,10,11} Meena Kumari,¹² Tellervo Korhonen,^{13,14,15} Satu Männistö,¹³ Pedro Marques-Vidal,¹⁶ Marika Kaakinen,^{17,18} Alana Cavadino,^{19,20} Iris Postmus,^{21,22} Lise Lotte N Husemoen,²³ Tea Skaaby,²³ Tarun Veer Singh Ahluwalia,^{24,25,26} Jorien L Treur,²⁷ Gonneke Willemsen,²⁷ Caroline Dale,²⁸ S Goya Wannamethee,² Jari Lahti,^{29,30} Aarno Palotie,^{31,32,33} Katri Räikkönen,²⁹ Alex McConnachie,³⁴ Sandosh Padmanabhan,³⁵ Andrew Wong,³⁶ Christine Dalgård,³⁷ Lavinia Paternoster,^{1,3} Yoav Ben-Shlomo,¹ Jessica Tyrrell,^{38,39} John Horwood,⁴⁰ David M Fergusson,⁴⁰ Martin A Kennedy,⁴¹ Ellen A Nohr,⁴² Lene Christiansen,⁴³ Kirsten Ohm Kyvik,³⁷ Diana Kuh,³⁶ Graham Watt,⁴⁴ Johan G Eriksson,^{15,30,45,46,47} Peter H Whincup,⁴⁸ Jacqueline M Vink,²⁷ Dorret I Boomsma,²⁷ George Davey Smith,^{1,3} Debbie Lawlor,^{1,3} Allan Linneberg,^{23,49,50} Ian Ford,³⁴ J Wouter Jukema,^{51,52,53} Chris Power,²⁰ Elna Hyppönen,^{20,54,55} Marjo-Riitta Jarvelin,^{17,18,56,57,58} Martin Preisig,⁵⁹ Katja Borodulin,¹⁵ Jaakko Kaprio,^{13,15,60} Mika Kivimäki,⁶¹ Blair H Smith,⁶² Caroline Hayward,⁶³ Pål R Romundstad,⁵ Thorkild I A Sørensen,^{3,24,64} Marcus R Munafò,^{3,4} Naveed Sattar⁶⁵

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For numbered affiliations see end of article.

Correspondence to

Professor Richard W Morris; richard.morris@bristol.ac.uk

ABSTRACT

Objectives: To investigate, using a Mendelian randomisation approach, whether heavier smoking is associated with a range of regional adiposity phenotypes, in particular those related to abdominal adiposity.

Design: Mendelian randomisation meta-analyses using a genetic variant (rs16969968/rs1051730 in the *CHRNA5-CHRNA3-CHRNB4* gene region) as a proxy for smoking heaviness, of the associations of smoking heaviness with a range of adiposity phenotypes.

Participants: 148 731 current, former and never-smokers of European ancestry aged ≥ 16 years from 29 studies in the consortium for Causal Analysis Research in Tobacco and Alcohol (CARTA).

Primary outcome measures: Waist and hip circumferences, and waist-hip ratio.

Results: The data included up to 66 809 never-smokers, 43 009 former smokers and 38 913 current daily cigarette smokers. Among current smokers, for each extra minor allele, the geometric mean was lower for waist circumference by -0.40% (95% CI -0.57% to -0.22%), with effects on hip circumference, waist-hip ratio and body mass index (BMI) being -0.31% (95% CI -0.42% to -0.19%), -0.08% (-0.19% to 0.03%) and -0.74% (-0.96% to -0.51%), respectively. In contrast, among never-smokers, these effects were higher by 0.23% (0.09% to 0.36%), 0.17% (0.08% to 0.26%), 0.07% (-0.01% to 0.15%) and 0.35% (0.18% to 0.52%), respectively. When adjusting the three central adiposity measures for BMI, the effects among current smokers changed direction and were higher by 0.14%

Strengths and limitations of this study

- This is a very large Mendelian randomisation study of the relationship between smoking and several anthropometric phenotypes relating to regional adiposity.
- Data included never, former and current smokers from a very wide spectrum of ages among 29 studies.
- By using a genetic variant associated with smoking heaviness as a proxy for smoking heaviness, bias from confounding is minimised and findings are not affected by reverse causality.
- Data for direct measures of fat, such as fat mass, and the biomarker leptin were available for only about one fifth of the participants whose weight, height, waist and hip were measured.
- Participants were exclusively of self-reported European ancestry, and were mostly recruited in European countries.

(0.05% to 0.22%) for waist circumference, 0.02% (-0.05% to 0.08%) for hip circumference and 0.10% (0.02% to 0.19%) for waist-hip ratio, for each extra minor allele.

Conclusions: For a given BMI, a gene variant associated with increased cigarette consumption was associated with increased waist circumference. Smoking in an effort to control weight may lead to accumulation of central adiposity.

INTRODUCTION

Tobacco is the single most important cause of preventable death globally: one in two young people taking up lifelong cigarette smoking will die of causes related to it.¹ Enormous efforts have gone into developing interventions for smoking cessation. Spontaneous cessation rates are low due to the high proportion of smokers who are dependent on nicotine, and effective treatments are still not widely available. One barrier to smoking cessation is the fear of weight gain. In a study of almost 2000 smokers in the USA, recruited into a trial of bupropion and/or nicotine inhalers to promote cessation, 50% of female and 26% of male smokers reported that gaining weight discouraged them from trying to quit,² while among adults in Finland, daily smokers were found to report more weight concerns than former smokers or occasional smokers.³

A genetic variant in the chromosome 15 *CHRNA5-CHRNA3-CHRNA4* gene region (rs16969968) codes for a functional amino acid change D398N in the nicotinic receptor $\alpha 5$ subunit. The SNP rs16969968, which is in perfect linkage disequilibrium with SNP rs1051730 in European populations, is associated with smoking quantity among smokers.⁴ The minor allele of this variant is associated with an average increase in smoking amount of one cigarette per day in smokers and increases in cotinine (a metabolite of nicotine) levels.^{5 6} It has also been found that the variant was associated with a lower mean body mass index (BMI),⁷⁻⁹ thus adding evidence that heavier smoking leads to lower BMI. The latter study also noted lower waist and hip circumferences among smokers with the variant.⁸ However, prior observational evidence suggests that waist circumference and waist-hip ratio may be higher in smokers than in non-smokers after adjusting for BMI.¹⁰ It has also been observed that smoking in adolescence predicts abdominal obesity in adulthood.¹¹ Moreover, heavy smokers exhibit greater central adiposity than light smokers, based on an analysis of middle-aged smokers of European ancestry.¹² These studies suggest that smoking leads to a central fat accumulation at the expense of peripheral fat loss, particularly in women.¹³ In addition, there are also suggestions that smoking may lead to loss of muscle mass as indicated by lower hip circumferences in smokers. This is of high public health relevance in view of the reportedly greater impact of increased central adiposity both on mortality^{14 15} and on the development of diabetes, especially among women,^{16 17} and since smoking is associated with an increased risk of type 2 diabetes.¹⁸

We previously used Mendelian randomisation methods to investigate the effect of smoking quantity on BMI.^{7 9} This method exploits Mendel's laws concerning the random assortment of alleles at the time of gamete formation so that individuals are allocated at random to having 0, 1 or 2 alleles in the rs1051730/rs16969968 genotype. The effect of this genotype on smoking quantity among smokers has been demonstrated,⁶ and thus the inverse relationship between allele count and BMI is not subject to effects of confounding and reverse causality. Using a

substantial pool of studies in the consortium for Causal Analysis Research in Tobacco and Alcohol (CARTA), we have extended our use of Mendelian randomisation methods to examine the effect of smoking quantity on a range of adiposity phenotypes. We test the hypotheses that (1) phenotypes representing central adiposity are affected by smoking quantity differentially from other phenotypes, and (2) these effects are more marked among women than among men.

METHODS

Study populations

We used data on individuals (≥ 16 years) of self-reported European ancestry from 29 studies from the CARTA consortium (<http://www.bris.ac.uk/expsych/research/brain/targ/research/collaborations/carta/>): the 1958 Birth Cohort (1958BC), the Avon Longitudinal Study of Parents and Children (ALSPAC, including both mothers and children), the British Regional Heart Study (BRHS), the British Women's Heart and Health Study (BWHHS), the Caerphilly Prospective Study (CaPS), the Christchurch Health and Development Study (CHDS), CoLaus, the Danish Monica study (Dan-MONICA), the Exeter Family Study of Child Health (EFSOCH), the English Longitudinal Study of Ageing (ELSA), the National FINRISK studies, GEMINAKAR, GS:SFHS (Generation Scotland: Scottish Family Health Study), the Genomics of Overweight Young Adults (GOYA) females, GOYA males, the Helsinki Birth Cohort Study (HBCS), Health2006, Health2008, the Nord-Trøndelag Health Study (HUNT), Inter99, MIDSPAN, the Northern Finland Birth Cohorts (NFBC 1966 and NFBC 1986), the National Health and Nutrition Examination Survey (NHANES), the MRC National Survey of Health & Development (NSHD), the Netherlands Twin Register (NTR), the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) and Whitehall II. All studies received ethics approval from the local research ethics committees. Further details of these studies are provided in online supplementary material.

Genotype

Within each study, individuals were genotyped for one of two single nucleotide polymorphisms (SNPs) in the *CHRNA5-A3-B4* nicotinic receptor subunit gene cluster, either rs16969968 or rs1051730. These SNPs are in perfect linkage disequilibrium with each other in Europeans ($R^2=1.00$ in HapMap 3, <http://hapmap.ncbi.nlm.nih.gov/>) and therefore represent the same genetic signal. Where studies had data available for both SNPs, we used the SNP that was genotyped in the largest number of individuals. Details of genotyping methods within each study are provided in online supplementary material.

Adiposity measures

Direct physical measurements included weight, height, waist and hip circumferences, arm circumference,

triceps skinfold and subscapular skinfold thickness. Fat mass and fat-free mass were available from bioimpedance measures, while leptin and adiponectin were the two biochemical markers related to fat mass.

BMI (weight/height²) and waist-hip ratio (waist/hip) were calculated.

Waist circumference and waist-hip ratio were taken as key measures of central adiposity, while BMI acted as a non-specific measure of adiposity for purposes of adjustment in regression analysis.

Smoking status

Smoking status was self-reported (either by questionnaire or interview) at the same time as regional adiposity measures for all studies, with the exception of 1958 BC (see online supplementary material). Individuals were classified as current, former, ever (ie, current and former combined) or never cigarette smokers. Where information on pipe and cigar smoking was available, individuals reporting being current or former smokers of pipes or cigars but not cigarettes were excluded from all analyses.

For studies with adolescent populations (ALSPAC children and NFBC 1986), analyses were restricted to current daily smokers who reported smoking at least one cigarette per day (current smokers) and individuals who had never tried smoking (never-smokers).

Statistical analysis

Analyses were conducted within each contributing study using Stata (Stata Corp, College Station, Texas, USA) and R (R Foundation for Statistical Computing, Vienna, Austria. <http://www.R-project.org>) software, following the same analysis plan. Analyses were restricted to individuals with full data on smoking status and rs1051730/rs16969968 genotype, and having data on at least one of the regional adiposity phenotypes.

Within each study, genotype frequencies were tested for deviation from the Hardy Weinberg Equilibrium (HWE) using a χ^2 test. Mendelian randomisation analyses of the association between rs1051730/rs16969968 and each regional adiposity phenotype were performed using linear regression, stratified by smoking status (never, former and current) and sex, and adjusted for age. Apart from height, natural logarithmic transforms were taken of every anthropometric phenotype. An additive genetic model was assumed on log values, so that each effect size could be exponentiated to represent the percentage increase per minor (risk) allele. These analyses were presented separately for each smoking status category. All phenotypic measures were further adjusted for log(BMI) (apart from weight, height and BMI itself), thus assessing the effect of the particular adiposity measure after adjusting for this global weight measure. Log(weight) was adjusted for height instead of log(BMI). Since adjustment for ratio variables in anthropometric studies has been criticised,¹⁹ we further adjusted waist circumference for log(weight) and height.

Finally, we repeated analysis of waist circumference adjusted for BMI restricted to participants with BMI under 30 kg/m²; 95% CIs have been quoted for all effect sizes.

Meta-analysis was also carried out of the relationship between reported daily cigarette consumption and rs1051730/rs16969968 genotype, among current smokers.

Although analyses were carried out separately for males and females, the estimates were combined where no evidence for separate sex effects was seen. For NHANES, which has a survey design, Taylor series linearisation was implemented to estimate variances. For studies including related family members, appropriate methods were used to adjust SEs: in GEMINAKAR, twin pair identity was included as a cluster variable in the model; in MIDSPAN, linear mixed effects regression models fitted using restricted maximum likelihood were used to account for related individuals, while in NTR, only unrelated individuals were included. ALSPAC mothers and children were analysed as separate samples; as there are related individuals across these samples, sensitivity analyses were performed excluding each of these studies in turn.

Results from individual studies were meta-analysed in Stata (V.13) using the 'metan' command from Stata. Where there was evidence of heterogeneity between studies ($I^2 > 50\%$), it was planned that both fixed and random effects analyses would be performed: however, as this never occurred, results for fixed effects analysis only are shown. Meta-regression analysis, using the 'metareg' command from Stata, was used to examine whether SNP effects varied by smoking status or by sex, or by a smoking by sex combination.

RESULTS

Descriptive statistics

The maximum sample size available, with genotype recorded, was 148 731 for weight, height and BMI over 29 studies. The data on individuals with weight, height, smoking status and genotype recorded included 66 809 never-smokers, 43 009 former smokers and 38 913 current smokers. Waist circumference was available in 28 studies (n=142 381), and hip circumference and waist-hip ratio in 25 studies (n=139 667). Measures of fat mass and fat-free mass were provided by 10 studies (n=28 231), arm circumference by nine studies (n=72 536), and skinfolds by five studies (n=7758). Finally, leptin and adiponectin were measured in nine studies (n=23 630 and 19 191, respectively). Overall, 47% of the combined study population was male. The median age within the contributing studies ranged from 16–74 years. Descriptive statistics for each of the study populations are found in the supplementary material (see online supplementary table S1).

Minor allele frequency for rs1051730/rs16969968 ranged between 0.31 and 0.36. There was no strong evidence for deviation from the Hardy-Weinberg

Equilibrium in any of the studies (p values all ≥ 0.09 , see online supplementary table S2).

Mendelian randomisation analysis

Table 1 shows the per-allele increases in each phenotype within each smoking status category. As previously shown,⁹ the increase in BMI was positive in never-smokers: +0.35% (95% CI 0.18% to 0.52%; $p=6.38\times 10^{-5}$), non-significant in former smokers: -0.14% (95% CI -0.34% to +0.07%; $p=0.19$) and significantly inverse in current smokers: -0.74% (95% CI -0.96% to -0.51%; $p=2\times 10^{-10}$). The full results for each contributing study are shown in online supplementary figure S1.

The waist circumference was higher per minor allele in never-smokers: +0.23% (95% CI 0.09% to 0.36%; $p=0.0012$), non-significantly related in former smokers -0.07% (95% CI -0.24% to 0.09%; $p=0.37$) and lower in current smokers -0.40% (95% CI -0.57 to -0.22 $p=1.69\times 10^{-5}$); differences among smoking groups were highly significant ($p=3.85\times 10^{-7}$; see online supplementary figure S2). The per-allele effect on waist circumference in current smokers was about half the magnitude of that seen for BMI. After adjustment for log(BMI), the minor allele of rs1051730-rs16969968 was not associated with waist circumference in either never-smokers: +0.01% (95% CI -0.06 to 0.08; $p=0.72$) or former smokers +0.06% (95% CI -0.02% to 0.15%; $p=0.15$). However, in current smokers, the minor allele was associated with a 0.14% (95% CI 0.05% to 0.22%; $p=0.003$) higher waist circumference after adjustment for log (BMI). Very similar results were seen in all three smoking status categories after waist was adjusted for log (weight) and height instead of for log(BMI). Effects of genotype on waist circumference were shown to differ between smoking status categories before adjustment ($p=3.85\times 10^{-7}$) but only weakly after adjustment for log (BMI) ($p=0.102$), and after adjustment for log(weight) and height ($p=0.018$). Little heterogeneity of study results was evident ($I^2\leq 25\%$ within all smoking groups). After restricting analysis to participants with BMI under 30 kg/m², we found that the percentage increases in waist circumference (after adjustment for log(BMI)) were 0.04% (95% CI -0.03% to 0.12%) for never-smokers, 0.03% (95% CI -0.06% to 0.13%) for ex-smokers and 0.12% (95% CI 0.02% to 0.21%) for current smokers: however, the test for difference in effects gave $p=0.41$.

Unadjusted results for hip circumference were very similar to that seen for waist, both in direction and magnitude, in all smoking status groups (see online supplementary figure S3). However, after adjustment for log (BMI), effects were not apparent in any of the three groups, and nor was the interaction of gene and smoking status.

Results for the waist-hip ratio were similar to the BMI, waist and hip circumferences in direction but were smaller in magnitude: +0.07%, 0.00% and -0.08%

increases in never-smokers, former smokers and current smokers, respectively ($p=0.083$ for differences between smoking categories; see online supplementary figure S4). After adjustment for log(BMI), increases remained non-significant for never-smokers and former smokers (-0.01% and 0.04%) but increased significantly among current smokers (0.10%) ($p=0.13$ for differences among smoking groups).

For several other phenotypes, per-allele decreases were observed in current smokers that exceeded those seen either in former or never-smokers (see online supplementary table S4). However, there was only statistical evidence for decreases among current smokers for arm circumference ($p=8.4\times 10^{-5}$) and leptin ($p=0.025$), while the difference between smoking groups was only significant for arm circumference ($p=3.29\times 10^{-4}$). Both effects became non-significant after adjustment for log(BMI). Fat mass and fat-free mass, after adjustment by height, showed differences in effects by smoking group. These effects were more due to per-allele increases seen among never-smokers than decreases among current smokers.

Meta-regression analyses showed no clear evidence for associations between genotype and each adiposity phenotype being modified by sex: p values exceeded 0.1 for all phenotypes, adjusted or unadjusted, apart from hip circumference. The per-allele decreases in hip circumference among current smokers appeared more marked among women ($p=0.067$), but this effect was no longer apparent after adjusting for BMI ($p=0.51$).

The mean difference in daily cigarette consumption was 0.77 among current smokers (95% CI 0.67 to 0.88, $I^2=17\%$).

DISCUSSION

This meta-analysis of 29 studies comprising almost 150 000 participants with key adiposity phenotypes has demonstrated, first, that a variant associated with increased cigarette consumption was associated not only with lower BMI among current smokers, consistent with earlier findings,^{7 8} but also with lower waist and hip circumferences. Second, the inverse association of the variant with lower waist circumference among current smokers changed direction after adjusting for BMI. The variant was positively associated with waist circumference but associated neither with hip circumference after BMI adjustment nor waist-hip ratio. Our results suggest that for every copy of the minor allele associated with cigarette consumption (ie, increasing cigarette per day consumption by approximately one cigarette), waist circumference will be increased by 0.14% if BMI were to remain constant. This suggests a preferential redistribution towards central adiposity associated with higher cigarette consumption: this important finding is in keeping with our hypothesis and extends current observational data.

We also observed that none of the effects were modified by sex, contrary to our second hypothesis. Finally,

Table 1 Per allele percentage increases in measures of regional adiposity (BMI, weigh, waist circumference, hip circumference, waist-hip ratio) among never, ex and current smokers, before and after adjustment for BMI

BMI (kg/m ²)	Adjusted for age			p For interaction*	Adjusted for age and BMI			p For interaction*
	Never-smokers	Former smokers	Current smokers		Never-smokers	Former smokers	Current smokers	
% increase	0.35	-0.14	-0.74	4.95×10 ⁻¹³	-			
95% CI	(0.18 to 0.52)	(-0.34 to 0.07)	(-0.96 to -0.51)					
p	6.38×10 ⁻⁵	0.19	2.00×10 ⁻¹⁰					
N	66 809	43 009	38 912					
I ²	14%	0%	0%					
Waist circumference (cm)								
% increase	0.23	-0.07	-0.40	3.85×10 ⁻⁷	0.01	0.06	0.14	0.087
95% CI	(0.09 to 0.36)	(-0.24 to 0.09)	(-0.57 to -0.22)		(-0.06 to 0.08)	(-0.02 to 0.15)	(0.05 to 0.22)	
p	0.0012	0.37	1.69×10 ⁻⁵		0.72	0.15	0.003	
N	64 265	40 756	37 360					
I ²	14%	0%	10%		0%	0%	13%	
Hip circumference (cm)								
% increase	0.17	-0.07	-0.31	1.79×10 ⁻⁹	0.02	0.02	0.02	0.99
95% CI	(0.08 to 0.26)	(-0.17 to 0.04)	(-0.42 to -0.19)		(-0.03 to 0.07)	(-0.04 to 0.08)	(-0.05 to 0.08)	
p	2.95×10 ⁻⁴	0.23	2.55×10 ⁻⁷		0.38	0.54	0.59	
N	62 323	40 512	36 833					
I ²	7%	0%	0%		16%	0%	0%	
Waist-hip ratio								
% increase	0.07	0	-0.08	0.083	-0.01	0.04	0.1	0.13
95% CI	(-0.01 to 0.15)	(-0.10 to 0.10)	(-0.19 to 0.03)		(-0.08 to 0.06)	(-0.04 to 0.13)	(0.02 to 0.19)	
p	0.087	0.97	0.14		0.78	0.30	0.02	
N	62 322	40 512	36 833					
I ²	21%	9%	15%		0%	0%	13%	

*Interaction assessed by assessing heterogeneity between effect estimates according to smoking status, with a fixed effects model.
BMI, body mass index.

we have already noted among never-smokers an unexpected positive association of the gene variant with BMI⁹: the current analysis demonstrates this same association with waist and hip circumferences. This occurred in the opposite direction to the inverse association of various adiposity measures with the gene variant seen in current smokers (before adjustment for BMI).

The analysis consisted of never, former and current smokers from a very wide spectrum of ages among the 29 studies. The sample size was very large for the primary phenotypes considered here. Participants were exclusively of self-reported European ancestry, and were mostly recruited in European countries. Data for direct measures of fat, such as fat mass, and the biomarker leptin were available for only about one-fifth of the participants whose weight, height, waist and hip were measured. Effects according to genotype for these phenotypes showed broadly similar results for the three smoking categories to those seen for BMI.

Mendelian randomisation has proved a powerful tool for eliciting causal associations between phenotypic measures.²⁰ In the present analysis, Mendel's laws concerning random assignment of genotype should produce an unconfounded comparison between the genotype influencing smoking consumption and the outcomes of interest, namely anthropometric phenotypes. Furthermore, since this random assignment occurs at the very outset of life, the associations between genotype and anthropometric measures cannot be due to reverse causality. If the genotype only influences smoking consumption, and not the initiation of smoking, then the relationship between genotype and anthropometric outcomes would only be expected among smokers.

In fact, while the variant was associated with lower waist and hip circumferences among current smokers, it was associated with greater waist and hip circumferences among never-smokers. This suggests that the true effect among current smokers may be even greater than estimated. When we adjusted waist circumference for BMI, there was no association with the gene variant among never-smokers. The relative proportions of ever-smokers and never-smokers were not clearly associated with genotype in the CARTA consortium, as reported elsewhere.⁹

The reversal of the association between waist circumference and allele count from negative to positive among current smokers after adjustment for BMI may be consistent with alternative explanations. First, heavy smokers may have less muscle mass; however, no association between allele count and fat-free mass could be detected in our analysis among smokers. Second, the test for interaction for smoking status and allele count on waist circumference after adjustment was of weak statistical significance. Third, the adjustment of one measure of adiposity with another with which it is highly correlated may have caused a spurious association. We repeated our analysis for participants with BMI under 30 only, where the correlation was more modest, and obtained similar results, albeit with reduced evidence for an effect.

Stratification of our analyses by smoking status could, in theory, introduce bias by conditioning on a collider (rs1051730/rs16969968).²¹ This variant shows some evidence for association with smoking cessation (current vs former smoking).²² While this is a possibility, no effect modifications of this variant with potential confounders by smoking status were demonstrated among 56 625 participants in the HUNT study.⁸

Cross-sectional observational data from Switzerland has demonstrated that waist and hip circumferences were more strongly related to the number of cigarettes smoked per day than was BMI,¹³ while in Scotland being a smoker was associated with greater central adiposity among women.¹² In a Finnish longitudinal twin cohort study, smoking in adolescence predicted abdominal obesity in adulthood.¹¹ Observational data are, however, prone to confounding and reverse causality, and the present study adds some evidence that the associations reported are likely to be causal.

Some observational studies have noted that low fat-free mass²³ and bone mineral density²⁴ were more common among smokers. The present analysis has not substantiated the association with fat-free mass, although our sample size was much more limited for this phenotype.

Our findings resonate with observational studies which have shown associations between smoking and risk of diabetes,^{17 18} especially as analysis of the British Women's Heart and Health Study showed that abdominal adiposity was a stronger predictor of diabetes than was BMI.¹⁶ Waist circumference and waist-to-hip ratio were strongly associated, independently of BMI, with the risk of death among 359 387 participants from nine countries in the European Prospective Investigation into Cancer and Nutrition.¹⁵ Therefore, the health hazards of smoking could well be enhanced or partly mediated through increasing abdominal adiposity. In addition, the desire of many smokers to use smoking as a means of weight control² might be counterproductive if a loss of weight is accompanied by a relative increase in waist circumference: this possibility could be used in counselling people seeking to quit smoking.

People who quit smoking appear to be at increased risk of acquiring diabetes in the short term but this was not explained by weight gain in a Japanese population.²⁵ This study took place almost exclusively among white European participants, and replication of the findings among other ethnic populations would be of great value. This is especially urgent on a global scale since smoking levels are increasing among several non-white ethnic groups, and this is seen to be partly responsible for increases in coronary heart disease mortality in Beijing, China,²⁶ in Syria²⁷ and in Tunisia among women.²⁸ In addition, increases in average waist circumference have been observed even when average BMI levels have remained constant,²⁹ and metabolic disorders, especially diabetes, have increased in prevalence.³⁰ It is thus possible that increased CHD mortality will be partly fuelled by increasing smoking levels.

Mendelian randomisation studies have more potential than traditional observational epidemiological studies to establish causality for specific exposures,²⁰ and they should now be used to investigate other impacts of smoking, in particular on pathways leading to type 2 diabetes, as well as on type 2 diabetes itself. The findings of this study could now be further tested by assembling data from randomised trials of smoking cessation, where postintervention data on measures of central adiposity are available. If confirmed, a tendency for smokers to acquire an ‘apple shape’ due to increasing central adiposity might provide a novel health promotion message to encourage smoking cessation, and appropriate new interventions should then be designed and evaluated as part of overall tobacco control policies in society.

Author affiliations

¹School of Social and Community Medicine, University of Bristol, Bristol, UK

²Department of Primary Care and Population Health, UCL, London, UK

³MRC Integrative Epidemiology Unit (IEU) at the University of Bristol, University of Bristol, Bristol, UK

⁴UK Centre for Tobacco and Alcohol Studies and School of Experimental Psychology, University of Bristol, Bristol, UK

⁵Department of Public Health, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway

⁶Forensic Department, Research Centre Brøset, St Olav's University Hospital Trondheim, Trondheim, Norway

⁷Department of Endocrinology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

⁸Department of Laboratory Medicine, Children's and Women's Health, The Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway

⁹Medical Genetics Section, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

¹⁰Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK

¹¹Queensland Brain Institute, University of Queensland, Brisbane, Queensland, Australia

¹²Institute for Social and Economic Research, University of Essex, Colchester, UK

¹³Department of Public Health, Hjelt Institute, University of Helsinki, Helsinki, Finland

¹⁴Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

¹⁵National Institute for Health and Welfare, Helsinki, Finland

¹⁶Department of Internal Medicine, Lausanne University Hospital, Lausanne, Switzerland

¹⁷Institute of Health Sciences, University of Oulu, Oulu, Finland

¹⁸Biocenter Oulu, University of Oulu, Oulu, Finland

¹⁹Centre for Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

²⁰Population, Policy and Practice, UCL Institute of Child Health, University College London, UK

²¹Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands

²²Netherlands Consortium of Healthy Ageing, Leiden, The Netherlands

²³Research Centre for Prevention and Health, the Capital Region of Denmark, Denmark

²⁴Novo Nordisk Foundation Center for Basic Metabolic Research, Section of Metabolic Genetics, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

²⁵Steno Diabetes Center, Gentofte, Denmark

²⁶COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev

and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark

²⁷Department of Biological Psychology, Netherlands Twin Register, VU University, Amsterdam, The Netherlands

²⁸Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK

²⁹Institute of Behavioural Sciences, University of Helsinki, Helsinki, Finland

³⁰Folkhälsan Research Centre, Helsinki, Finland

³¹Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge, UK

³²Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Finland

³³The Medical and Population Genomics Program, The Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA

³⁴Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK

³⁵Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

³⁶MRC Unit for Lifelong Health and Ageing at UCL, London, UK

³⁷Department of Environmental Medicine, Institute of Public Health, University of Southern Denmark, Odense, Denmark

³⁸European Centre for Environment and Human Health, University of Exeter Medical School, Truro, UK

³⁹Genetics of Complex Traits, University of Exeter Medical School, Exeter, UK

⁴⁰Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

⁴¹Department of Pathology, University of Otago, Christchurch, New Zealand

⁴²Institute for Clinical Research, University of Southern Denmark, Odense, Denmark

⁴³Department of Epidemiology, Biostatistics and Biodemography, Institute of Public Health, University of Southern Denmark, Denmark

⁴⁴University of Glasgow, Glasgow, UK

⁴⁵Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland

⁴⁶Unit of General Practice, Helsinki University Central Hospital, Helsinki, Finland

⁴⁷Vasa Central Hospital, Vasa, Finland

⁴⁸Population Health Research Institute, St George's University of London, London, UK

⁴⁹Department of Clinical Experimental Research, Glostrup University Hospital, Glostrup, Denmark.

⁵⁰Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

⁵¹Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

⁵²Durrer Center for Cardiogenetic Research, Amsterdam, The Netherlands

⁵³Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands

⁵⁴Centre for Population Health Research, School of Health Sciences and Sansom Institute of Health Research, University of South Australia, Adelaide, Australia

⁵⁵South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia

⁵⁶Unit of Primary Care, Oulu University Hospital, Oulu, Finland

⁵⁷Department of Children and Young People and Families, National Institute for Health and Welfare, Oulu, Finland

⁵⁸Department of Epidemiology and Biostatistics, MRC Health Protection Agency (HPA) Centre for Environment and Health, School of Public Health, Imperial College London, London, UK

⁵⁹Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland

⁶⁰Institute for Molecular Medicine Finland FIMM, University of Helsinki, Helsinki, Finland

⁶¹Department of Epidemiology and Public Health, University College London, London, UK

⁶²Division of Population Health Sciences, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK

⁶³Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

⁶⁴Institute of Preventive Medicine, Bispebjerg and Frederiksborg Hospitals, The Capital Region, Copenhagen, Denmark

⁶⁵Faculty of Medicine, BHF Glasgow Cardiovascular Research Centre, Glasgow, UK

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Ethics approval was granted for the BWHHS from the London Multi-Centre Research Ethics Committee and 23 Local Research Ethics Committees. **CaPS:** The Caerphilly Prospective Study was conducted by the former MRC Epidemiology Unit (South Wales). The Caerphilly archive is now maintained by the School of Social and Community Medicine in Bristol University. We thank the Health and Social Care Information Centre (HSCIC) for helping us maintain long-term follow-up with the cohort. We thank all the men who have given their time to be participants in CaPS. 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Collaborators Allan Linneberg.

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Ethics approval The manuscript describes approval given for each of the 29 studies.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement 1958BC: This study makes use of data generated by the Wellcome Trust Case-Control Consortium. A full list of investigators who contributed to generation of the data is available from the Wellcome Trust Case-Control Consortium website. The 1958 birth cohort data can be accessed via the UK Data Service (<http://ukdataservice.ac.uk/>). ALSPAC: Data used for this submission will be made available on request to the ALSPAC executive committee (alspac-exec@bristol.ac.uk). The ALSPAC data management plan (available here: <http://www.bristol.ac.uk/alspac/researchers/data-access/>) describes in detail the policy regarding data sharing, which is through a system of managed open access. BRHS: We welcome proposals for collaborative projects and data sharing (<http://www.ucl.ac.uk/pcph/research-groups-themes/brhs-pub>). For general data sharing enquiries, please contact Lucy Lennon (l.lennon@ucl.ac.uk). BWHHS: All BWHHS data collected are held by the research team based at the London School of Hygiene and Tropical Medicine for ongoing analysis. If you would like to collaborate with the BWHHS team, contact the study coordinator, AA (antoinette.amuzu@lshtm.ac.uk). Data and biological samples provided to the collaborators can only be used for the purposes originally stated and must not be used in any other way without re-application to the BWHHS team.

No data should be passed on to any third party unless they were specified in the original application. CaPS: Data used for the Caerphilly Prospective study (CaPS) was made available by the CaPS access committee (Chair: Professor Kay Tee Khaw). More information about its managed access procedure is available on the study website (<http://www.bris.ac.uk/social-community-medicine/people/project/1392>). CHDS: Data contributed for this submission are available on request from the CHDS (john.horwood@otago.ac.nz). ColaUS/PsyCoLaus: Data from the ColaUS/PsyCoLaus study can be requested according to the procedure described on the CoLaus website (http://www.colaus.ch/en/cls_home/cls_pro_home/cls-research-3.htm). ELSA: ELSA data are made available through the ESDS website (<http://www.elsa-project.ac.uk/availableData>). FINRISK: Data used for this submission will be made available on request to the FINRISK Management Group, according to the given ethical guidelines and Finnish legislation. Generation Scotland: Data are available on request (access@generationscotland.org). GOYA females: An anonymised copy of the data used for this submission will be made available on request to the GOYA analysts after permission has been given by the DNBC executive committee (www.dnbc.dk). HBCS: Data used for this submission will be made available on request to the HBCS executive committee (johan.eriksson@helsinki.fi). Health2006/Health2008/Inter99: Data used for this submission can be made available on request to the Research Centre for Prevention and Health (<http://www.regionh.dk/fcfs/Menu/>). Please contact LLNH (lise.lotte.nystrup@regionh.dk) or AL (allan.linneberg@regionh.dk). HUNT: Data used from the HUNT Study for this submission will be made available on request to the HUNT Data Access Committee (hunt@medisin.ntnu.no). The HUNT data access information (<http://www.ntnu.edu/hunt/data>) describes in detail the policy regarding data availability. NFBC: Data used for this submission can be made available on request to Tuula Ylitalo (tuula.ylitalo@oulu.fi), Minna Mannikko (minna.annikko@oulu.fi) or M-RJ (m.jarvelin@imperial.ac.uk). NHANES: NHANES data can be accessed here: (<http://www.cdc.gov/nchs/nhanes.htm>). The genotype used in this analysis is a restricted variable. Applications for access to these data must be made through the Research Data Center: (<http://www.cdc.gov/rdc/>). NSHD: The NSHD data are made available to researchers who submit data requests (tomrclha.swifinfo@ucl.ac.uk). More information is available in the full policy documents (<http://www.nshd.mrc.ac.uk/data.aspx>). Managed access is in place for this study to ensure that use of the data is within the bounds of consent given previously by participants, and to safeguard any potential threat to anonymity since the participants are all born in the same week. NTR: Data used for this submission will be made available on request to the NTR committee (ntr@psy.vu.nl). Whitehall: Data from the Whitehall II study are made publicly available as described in the Whitehall II data sharing policy (<http://www.ucl.ac.uk/whitehallII/datasharing>).

TIAS, MRM and NS are joint senior authors.

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REFERENCES

- Doll R, Peto R, Boreham J, *et al*. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004;328:1519.
- Clark MM, Hurt RD, Croghan IT, *et al*. The prevalence of weight concerns in a smoking abstinence clinical trial. *Addict Behav* 2006;31:1144–52.
- Luostarinen M, Tuovinen EL, Saarni SE, *et al*. Weight concerns among Finnish ever-smokers: a population-based study. *Nicotine Tobacco Res* 2013;15:1696–704.
- Thorgeirsson TE, Geller F, Sulem P, *et al*. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature* 2008;452:638–42.
- Keskitalo K, Broms U, Heliövaara M, *et al*. Association of serum cotinine level with a cluster of three nicotinic acetylcholine receptor genes (CHRNA3/CHRNA5/CHRNA4) on chromosome 15. *Hum Mol Genet* 2009;18:4007–12.
- Munafò MR, Timofeeva MN, Morris RW, *et al*. Association between genetic variants on chromosome 15q25 locus and objective measures of tobacco exposure. *J Natl Cancer Inst* 2012;104:740–8.
- Freathy RM, Kazeem GR, Morris RW, *et al*. Genetic variation at CHRNA5-CHRNA3-CHRNA4 interacts with smoking status to influence body mass index. *Int J Epidemiol* 2011;40:1617–28.
- Asvold BO, Bjørngaard JH, Carslake D, *et al*. Causal associations of tobacco smoking with cardiovascular risk factors: a Mendelian randomization analysis of the HUNT Study in Norway. *Int J Epidemiol* 2014;43:1458–70.
- Taylor AE, Morris RW, Fluharty ME, *et al*. Stratification by smoking status reveals an association of CHRNA5-A3-B4 genotype with body mass index in never smokers. *PLoS Genet* 2014;10:e1004799.
- Kim JH, Shim KW, Yoon YS, *et al*. Cigarette smoking increases abdominal and visceral obesity but not overall fatness: an observational study. *PLoS ONE* 2012;7:e45815.
- Saarni SE, Pietiläinen K, Kantonen S, *et al*. Association of smoking in adolescence with abdominal obesity in adulthood: a follow-up study of 5 birth cohorts of Finnish twins. *Am J Public Health* 2009;99:348–54.
- Akbaritabartoori M, Lean ME, Hankey CR. Relationships between cigarette smoking, body size and body shape. *Int J Obes (Lond)* 2005;29:236–43.
- Clair C, Chioloro A, Faeh D, *et al*. Dose-dependent positive association between cigarette smoking, abdominal obesity and body fat: cross-sectional data from a population-based survey. *BMC Public Health* 2011;11:23.
- Bigaard J, Tjønneland A, Thomsen BL, *et al*. Waist circumference, BMI, smoking, and mortality in middle-aged men and women. *Obes Res* 2003;11:895–903.
- Pischon T, Boeing H, Hoffmann K, *et al*. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008;359:2105–20.
- Taylor AE, Ebrahim S, Ben-Shlomo Y, *et al*. Comparison of the associations of body mass index and measures of central adiposity and fat mass with coronary heart disease, diabetes, and all-cause mortality: a study using data from 4 UK cohorts. *Am J Clin Nutr* 2010;91:547–56.
- Wannamethee SG, Papacosta O, Whincup PH, *et al*. Assessing prediction of diabetes in older adults using different adiposity measures: a 7 year prospective study in 6,923 older men and women. *Diabetologia* 2010;53:890–8.
- Willi C, Bodenmann P, Ghali WA, *et al*. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2007;298:2654–64.
- Allison DB, Paultre F, Goran MI, *et al*. Statistical considerations regarding the use of ratios to adjust data. *Int J Obes Relat Metab Disord* 1995;19:644–52.
- Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* 2003;32:1–22.
- Cole SR, Platt RW, Schisterman EF, *et al*. Illustrating bias due to conditioning on a collider. *Int J Epidemiol* 2010;39:417–20.
- Taylor AE, Munafò MR, CARTA consortium. Commentary: does mortality from smoking have implications for future Mendelian randomization studies? *Int J Epidemiol* 2014;43:1483–6.
- Castillo EM, Goodman-Gruen D, Kritiz-Silverstein D, *et al*. Sarcopenia in elderly men and women: the Rancho Bernardo study. *Am J Prev Med* 2003;25:226–31.
- Ward KD, Klesges RC. A meta-analysis of the effects of cigarette smoking on bone mineral density. *Calcif Tissue Int* 2001;68:259–70.
- Oba S, Noda M, Waki K, *et al*. Smoking cessation increases short-term risk of type 2 diabetes irrespective of weight gain: the Japan Public Health Center-Based Prospective Study. *PLoS One* 2012;7:e17061.
- Cheng J, Zhao D, Zeng Z, *et al*. The impact of demographic and risk factor changes on coronary heart disease deaths in Beijing, 1999–2010. *BMC Public Health* 2009;9:30.
- Rastam S, Al AR, Maziak W, *et al*. Explaining the increase in coronary heart disease mortality in Syria between 1996 and 2006. *BMC Public Health* 2012;12:754.
- Saidi O, Ben MN, O'Flaherty M, *et al*. Analyzing recent coronary heart disease mortality trends in Tunisia between 1997 and 2009. *PLoS ONE* 2013;8:e63202.
- Chan JC, Malik V, Jia W, *et al*. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009;301:2129–40.
- Danaei G, Finucane MM, Lu Y, *et al*. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 2011;378:31–40.