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Case–Control Study of Congenital Anomalies: Study Methods and Nonresponse Bias Assessment

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ABSTRACT

Background: To describe the methods of a congenital anomalies case–control study conducted in New Zealand, discuss the encountered methodological difficulties, and evaluate the potential for nonresponse bias.

Methods: The potential cases ($n = 2710$) were New Zealand live births in 2007–2009 randomly selected from the New Zealand Congenital Anomalies Registry. The potential controls ($n = 2989$) included live births identified from the Maternity and Newborn Information System, frequency matched to cases by the child's year of birth and sex. Mothers were invited to complete an interview covering demographic, lifestyle, and environmental factors. Response probabilities for case and control mothers were evaluated in relation to maternal age, deprivation, occupation, and ethnicity, available from the Electoral Roll, and inverse probability weights (IPWs) for participation were calculated. Odds ratios (ORs) for key demographic and selected risk factors were estimated through unconditional logistic regression, with and without IPW.

Results: A total of 652 (24%) of case mothers and 505 (17%) of control mothers completed the interview. Younger and more deprived mothers were underrepresented among the participants, particularly for controls, resulting in inflated ORs of associations with congenital anomalies for younger age, Māori ethnicity, deprivation, and risk factors under study, such as blue-collar occupations and smoking, indicative of nonresponse bias. Nonresponse bias was minimized through IPW, resulting in ORs and exposure prevalence estimates similar to those based on the prerecruitment sample.

Conclusions: Attaining high participation rates was difficult in this study that was conducted in new mothers, particularly for the controls. The resulting nonresponse bias was minimized through IPW.

†Andrea 't Mannetje passed away in 2023, but played a leading role in all aspects of the study design, data collection, and drafting of this paper.

1 | Introduction

Congenital anomalies (CAs), or birth defects, affect ~4.5% of all babies born in New Zealand (NZ), a rate similar to that of other high-income countries (Christianson et al. 2006). CAs are highly variable in impact and severity and may affect the nervous, circulatory, digestive, genital, urinary, and musculoskeletal systems. Several genetic risk factors have been identified, including chromosomal abnormalities accounting for approximately 6% of CA in high-income counties, and single-gene defects accounting for approximately 7.5% (Christianson et al. 2006). Other risk factors include low folic acid intake, alcohol consumption, smoking, certain drugs and medications, some infections, obesity, and uncontrolled diabetes. An estimated 5%–10% of CA are due to exposure to known teratogens and 20%–30% to gene–environment interactions (Christianson et al. 2006). For ~50% of pregnancies affected by CA, a specific cause cannot be identified (Christianson et al. 2006), and more studies are therefore needed to identify additional opportunities for the primary prevention of CA.

Case–control studies offer a feasible way to attain sufficient study power and allow for a wide range of risk factors to be examined but involve methodological challenges (Tinker et al. 2015; Petersen et al. 2023) that require careful study design and conduct. Achieving high participation rates is particularly challenging, considering new mothers' busy schedules, low motivation for study participation in mothers of healthy infants, and a more general reduction in study participation rates (de Leeuw and de Heer 2002).

Here we describe the protocol of a case–control study conducted in NZ that aims to elucidate the role of a range of potential modifiable risk factors for CA, with a focus on occupational factors. Its specific challenges are discussed, and a detailed nonresponse bias assessment is presented.

2 | Methods

2.1 | Study Design and Aims

This population-based case–control study included live births in NZ in 2007, 2008, and 2009. Participation involved the mother, and where possible the father, completing an interview either by telephone or face to face. The focus was on modifiable risk factors, with a particular emphasis on occupational exposures.

The aims were to:

1. Assess associations between maternal and paternal occupational exposures and CA;
2. Assess the contribution of nonoccupational modifiable risk factors including obesity, diabetes, alcohol consumption, and folic acid supplementation;
3. Assess the contributions of (i) acute exposures during the critical period around conception and (ii) chronic lifetime exposures to CA risk;
4. Assess risk factors for specific CA subtypes;
5. Estimate the fraction of CA cases that can be potentially prevented.

2.2 | Case and Control Selection

Cases were identified from the NZ Congenital Anomalies Registry, "Te Tari Manaaki Haua" (NZCAR) (formerly the NZ Birth Defects Registry). NZCAR, a full member of the International Clearinghouse for Birth Defects Surveillance Research (https://www.ehinz.ac.nz/new-zealand-congenital-anomalies-registry/), was established in 1977 to routinely ascertain all live births with a diagnosed birth defect among newborns and those requiring treatment in public hospitals. The data is extracted from the national public hospital database (the National Minimum Dataset, NMDS).

Cases comprised a random sample of all births in 2007, 2008, and 2009 on NZCAR ($n = 2710$, sample size based on an assumed 30% participation rate), diagnosed with the eligible ICD-9 codes (listed in Supporting Information: eTable 1). Not eligible were all chromosomal abnormalities, common CA considered to be mild (e.g., undescended testes, which, if included, would have dominated the case group), and nonspecific CA. Cases with multiple diagnoses were included, provided that one diagnosis was eligible. Case mothers were invited using a two-step process: (1) obtaining consent (and telephone number of the mother) from their general practitioner (GP) to contact them and (2) invitation by mail followed by telephone invitation if after two mailed invitations there was no initial response and a telephone number was available. The GP consent stage for cases was included due to the sensitive nature of the study topic. If the GP of the mother considered that her participation in the study was in any way harmful to her or her family, the mother was not contacted.

The controls ($n = 2988$, sample size based on an assumed 30% participation rate) were identified from the Maternity and Newborn Information System, frequency matched by year of birth and sex. Controls with any CA were excluded through comparison with NZCAR. Mothers of controls were identified through data linkage with medical records and invited using a 1-step process through invitation by mail followed by telephone invitation if after three mailed invitations there was no response and a telephone number was available.

For 15.5% of cases, more than one ICD9-CA diagnoses eligible for inclusion were recorded on the NZCAR.

2.3 | Study Questionnaire

The questionnaire (see the Data S1) consisted of:

1. A general section involving information about the mother's demographics, that is, date of birth, ethnicity, highest achieved education, place of birth, parental occupation, residential history; height and weight; body shape at different ages using a pictorial; diet history; smoking history; alcohol history; lifetime work history; and medical history.
2. A pregnancy-specific section covering the critical period around the conception of the child, including information

about: the home and home-related exposures; use of hair dyes; dentist visits; hobbies; occupation and occupational exposures (a specialized agriculture questionnaire was completed if the mother worked in agriculture during or 3 months before pregnancy); medical conditions; medication use; alcohol consumption; smoking; use of recreational drugs; and nutrition and use of food supplements.

For the pregnancy-specific section, each question was asked for each of the four following time periods: 3 months prior to pregnancy, and the first, second, and third trimesters. To help identify the dates that defined these periods, a pregnancy timeline was completed (see Figure 1) and used during the interview to improve recall accuracy. The pregnancy timeline and the lifetime work history were sent prior to the interview to help reduce interview time and burden.

2.4 | Interviewers and Interviewer Training

An interviewer manual was developed covering: (1) the background of the study, (2) the purpose of each question, (3) "do's" and "do not's" when conducting the interview, and (4) examples of how interviewer and non-responder bias can be introduced and how to prevent it. An interviewer training day covered the interviewers' manual, the questionnaire, and guidance and resources for dealing with sensitive issues such as loss and having a child with a birth defect from representatives from relevant support organizations. All interviewers who worked on the study interviewed both case and control mothers.

2.5 | Field Work

Case mothers were not contacted within the first year to avoid burdening the mothers soon after the birth. The same was applied for control mothers to ensure that the time between birth and interview was similar for cases and controls. The secondary method of contact was a telephone call follow-up. For case mothers, telephone numbers were often provided by the GP for the majority, and for control mothers, telephone numbers were identified using tele-matching conducted by an external company, based on name and address. Overall, telephone numbers were available for ~25% of control mothers.

The interview was conducted either face to face or by telephone, according to the preference of the mother. Twenty-two percent of cases and 17% of control mothers opted for a face-to-face interview. Fathers were contacted for an interview at a later stage if the consent of the mother was obtained.

Interviews took place between November 2009 and November 2014. The mean time lag between birth and interview was 3.8 years for cases and 4.7 for controls. This difference was mainly due to the longer time it took to obtain up-to-date addresses and telephone numbers of control mothers.

2.6 | Statistical Analyses

Data were analyzed using SAS. A nonresponse bias assessment was conducted, through the use of inverse probability weights (IPWs) by modeling the probability of study participation for cases and controls in relation to the mother's age, area-level deprivation, ethnicity, and occupation as extracted from the NZ Electoral Roll. Unconditional logistic regression was applied to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the wide range of potential risk factors collected in the questionnaire.

2.7 | Ethics

Ethical approval was obtained from the NZ Multi-region Ethics Committee (MEC/07/08/113).

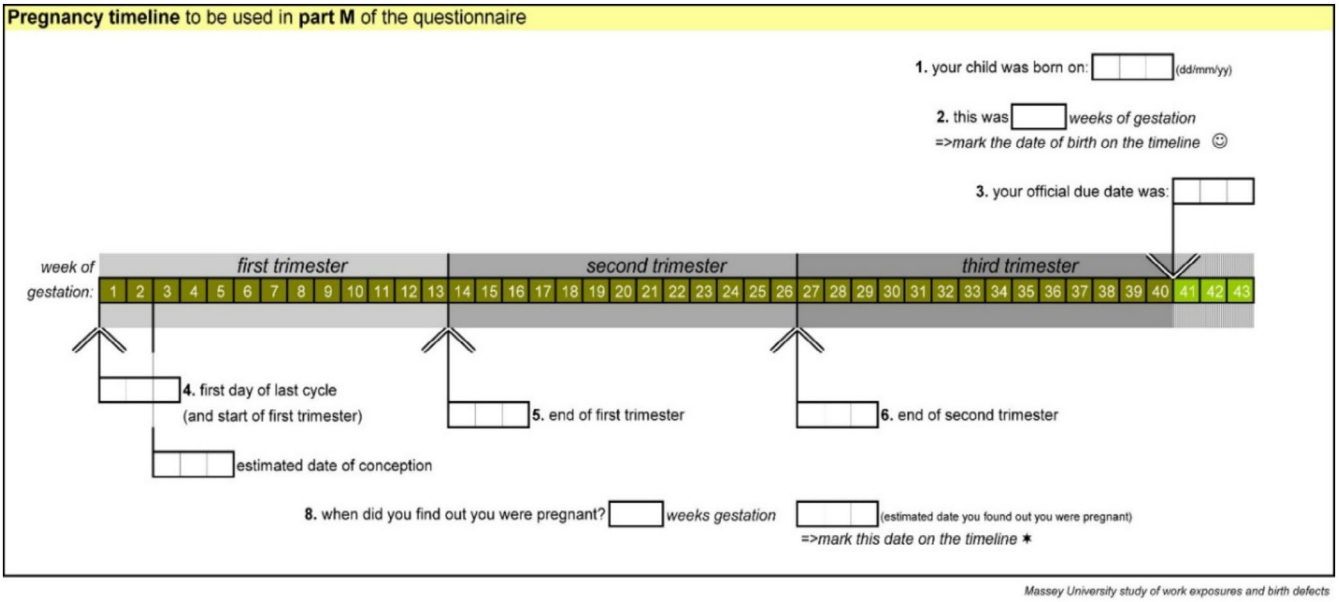

FIGURE 1 | Pregnancy timeline for the pregnancy-specific section of the questionnaire used to assist with recall for the questions related to the 3 months before the pregnancy and for each of the pregnancy trimesters [based on (Tobias and Huang 2007; Monge et al. 2004)].

3 | Results

3.1 | Response of Cases and Controls

Each of the 2710 potential cases and 2989 potential controls (the "prerecruitment sample") were assigned a response indicator, as represented in Figure 2. The contact rate (percentage of prerecruitment sample) was similar for cases (36%) and controls (33%). Of those that could be contacted, refusals were higher for controls (49%) than for cases (32%). The overall participation rate (number of participants/prerecruitment sample) was 24% for cases and 17% for controls. Due to the 2-step process of contacting the cases, cases also received an indicator for GP response: (1) GP consent, (2) GP refusal, (3) GP determined the case ineligible (e.g., GP was unable to contact the mother or mother no longer in NZ), (4) GP did not respond, and (5) GP could not be identified.

Fathers were only contacted if consent was obtained from mothers. Fathers' participation rates (as a percentage of participating and consenting mothers) were similar for cases (36%) and controls (37%).

3.2 | Response Probabilities by Key Characteristics

Mothers in the prerecruitment sample were linked to the Electoral Roll to obtain the following key characteristics for both participants and nonparticipants: (1) NZ Deprivation Index (NZDEP, which combines nine census variables reflecting aspects of material and social deprivation by mesh-block) based on address, (2) year of birth, (3) occupation (coded using the NZ Standard Classification of Occupations (NZSCO) 1-digit groups (Statistics New Zealand 2001)), and (4) Māori ethnicity (indigenous people of NZ; ~15% of the population at the time of the study).

The GP response profile is shown in Supporting Information: eFigure 1. A response was less likely to be received from the GP for mothers in the most deprived groups and for younger mothers. However, differences in GP consent rates (of the GP consents + refusals) were not observed for these variables. The response profile for mothers by each characteristic is provided in Supporting Information: eTable 2. The two steps involved in achieving the overall participation rates were (1) contact rate—percentage of the total prerecruitment sample we were

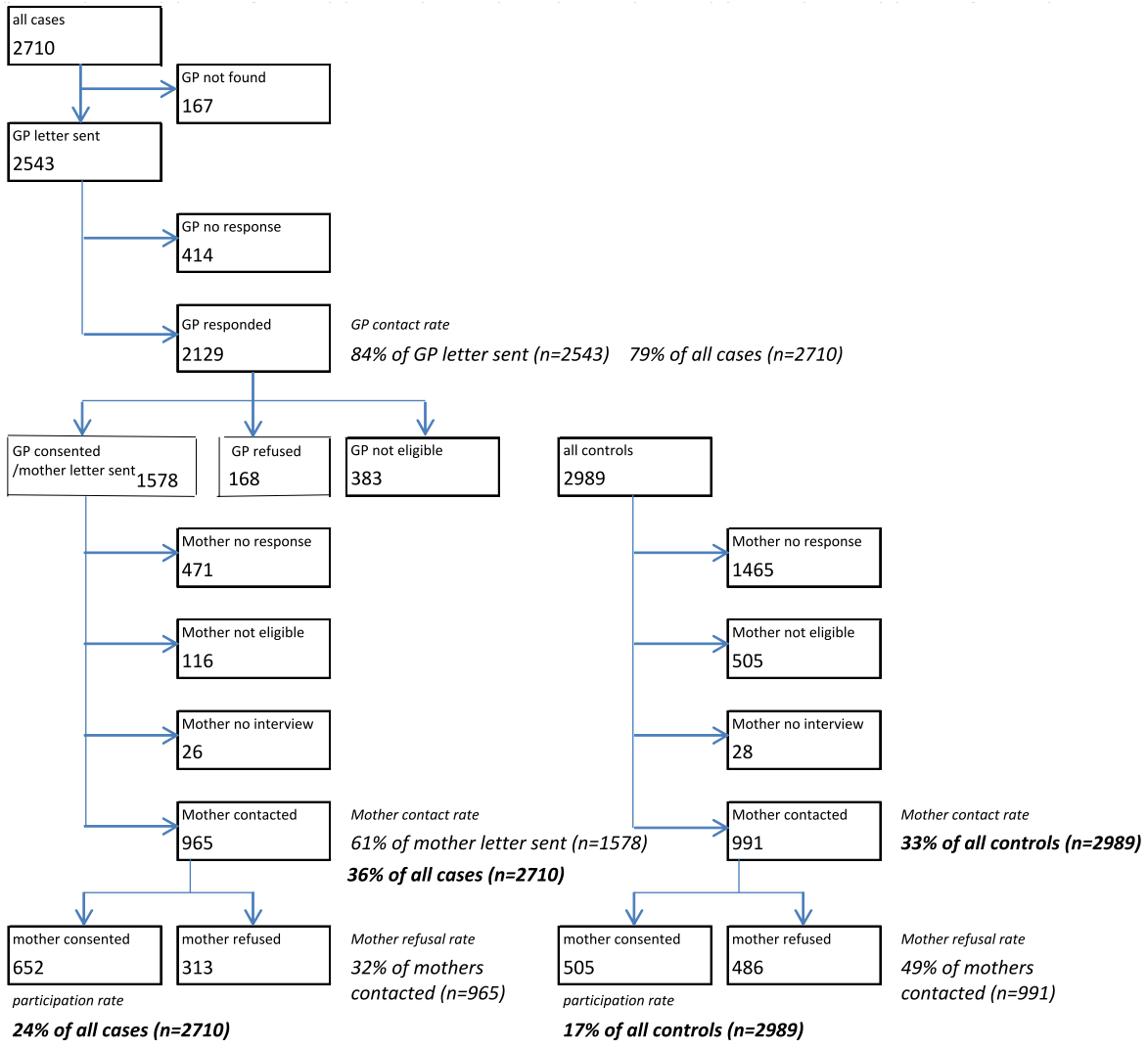

FIGURE 2 | Flow chart of case and control response.

able to contact and (2) refusal rate—percentage of all contacted. Figure 3 illustrates that higher area-level deprivation and younger age of the mother were associated with a lower contact rate; notably, steeper gradients were observed for controls. The highest contact rate was achieved for the oldest age group (born 1958–1975) (close to 50% for both cases and controls) and the lowest for the youngest age group (born 1985–1995) (10% for controls and 20% for cases). Refusal rates were not associated with area-level deprivation and only weakly associated with mother's age.

3.3 | Inverse Probability Weighting

Because younger and more deprived mothers were underrepresented among the participating cases and controls (Figure 3), IPWs were calculated. A weight was calculated for each participant, inversely proportional to the probability of participating, given the four key baseline characteristics of the mother: (1) NZDEP categorized as quintiles (from least deprived 1–2; 3–4; 5–6; 7–8; to most deprived: 9–10), (2) year of birth categories (1958–1975; 1975–1980; 1980–1985;1985–1995), (3) occupation (white collar: NZSCO 1-digit groups 1–4; blue collar: NZSCO 1-digit groups 5–9; and not in paid employment), and (4) Māori ethnicity (yes/no). Weights were obtained through logistic regression using the participation indicator (yes/no) as the outcome, regressed on the four key baseline characteristics, separately for cases and controls. This resulted in a propensity score for each individual, which can be interpreted as the probability that a person with a particular set of characteristics participates in the study given the determinants in the model. To obtain the IPWs, the propensity scores were inverted, and averaged to 1 for all participating cases and controls combined. This allowed the study data to be standardized to the distribution of characteristics in the initial (prerecruitment) sample.

Table 1 shows differences in participation by population characteristics and case/control status and provides a comparison of: ORs (odds of a given demographic characteristic in cases vs. controls) based on the prerecruitment sample (OR1 in Table 1), ORs based on those that could be contacted including the refusals (OR2),

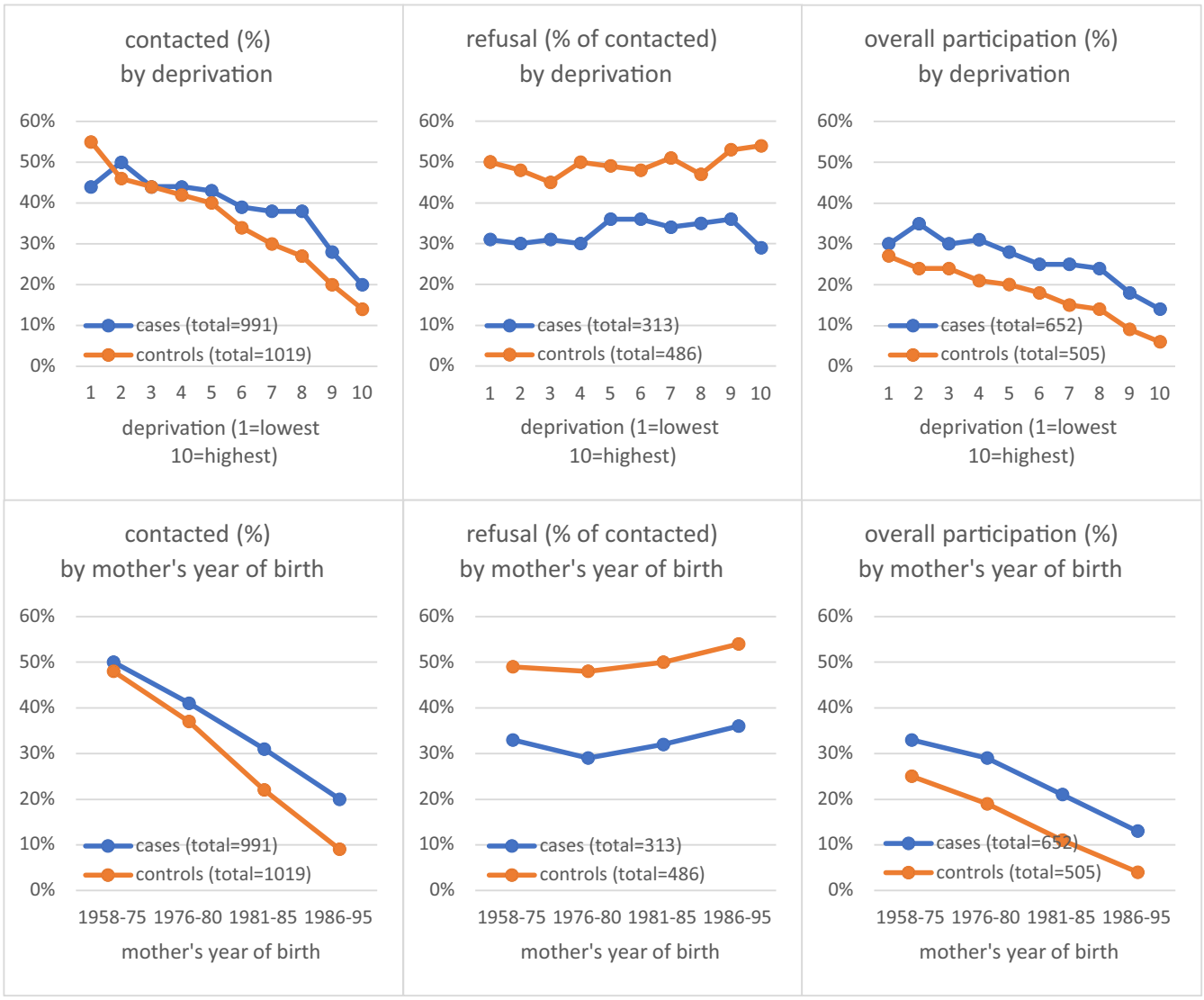

FIGURE 3 | Response probabilities by deprivation index and age of the mother.

TABLE 1 | Effect of nonresponse bias on the ORs for key baseline characteristics, and effectiveness of inverse probability weighting.

	(1) Whole prerecruitment sample				(2) Only contacted				(3) Only participants				(4) Only participants: mutually adjusted				(5) Only participants: weighted			
	Controls	Cases	OR1	95% CI	Controls	Cases	OR2	96% CI	Controls	Cases	OR3	95% CI	Controls	Cases	OR4	95% CI	Controls	Cases	OR5	95% CI
Deprivation (NZDEP)																				
Least deprived (1, 2)	498	448	1.0	Ref	255	217	1.0	Ref	128	149	1.0	Ref	128	149	1.0	Ref	128	149	1.0	Ref
(3, 4)	485	448	1.0	0.9–1.2	214	199	1.1	0.8–1.4	110	137	1.1	0.8–1.5	110	137	1.0	0.7–1.5	110	137	0.9	0.6–1.4
(5, 6)	615	485	0.9	0.7–1.0	229	206	1.1	0.8–1.4	116	129	1.0	0.7–1.3	116	129	0.9	0.6–1.3	116	129	0.8	0.6–1.2
(7, 8)	634	533	0.9	0.8–1.1	185	206	1.3	1.0–1.7	92	133	1.2	0.9–1.8	92	133	1.1	0.8–1.6	92	133	0.9	0.6–1.3
Most deprived (9, 10)	757	657	1.0	0.8–1.1	136	163	1.4	1.1–1.9	59	104	1.5	1.0–2.3	59	104	1.2	0.8–1.9	59	104	0.9	0.6–1.4
Missing	0	139			0	0							0	0			0	0		
Age (year of birth) of mother																				
Youngest (1985–1995)	510	366	1.0	Ref	49	82	1.0	Ref	21	49	1.0	Ref	21	49	1.0	Ref	21	49	1.0	Ref
(1980–1985)	646	418	0.9	0.8–1.1	153	132	0.5	0.3–0.8	73	88	0.5	0.3–0.9	73	88	0.6	0.4–1.1	73	88	0.9	0.6–1.4
(1975–1980)	784	523	0.9	0.8–1.1	296	220	0.4	0.3–0.7	151	155	0.4	0.3–0.8	151	155	0.6	0.3–1.0	151	155	1.0	0.7–1.5
Oldest (1958–1975)	1049	863	1.1	1.0–1.3	521	434	0.5	0.3–0.7	260	286	0.5	0.3–0.8	260	286	0.6	0.3–1.1	260	286	1.4	1.0–2.0
Missing	0	540	—		0	123			0	74	—		0	74			0	74	—	
Occupation mother																				
White collar (1–4)	1112	930	1.0	Ref	571	482	1.0	Ref	315	329	1.0	Ref	315	329	1.0	Ref	315	329	1.0	Ref
Blue collar (5–9)	640	477	0.9	0.8–1.0	203	210	1.2	1.0–1.5	91	148	1.6	1.2–2.1	91	148	1.6	1.1–2.2	91	148	0.9	0.7–1.2
Not paid employ	830	744	1.1	0.9–1.2	211	256	1.4	1.2–1.8	97	174	1.7	1.3–2.3	97	174	1.6	1.2–2.2	97	174	0.9	0.7–1.1

(Continues)

TABLE 1 | (Continued)

	(1) Whole prerecruitment sample				(2) Only contacted				(3) Only participants				(4) Only participants: mutually adjusted				(5) Only participants: weighted			
	Controls	Cases	OR1	95% CI	Controls	Cases	OR2	96% CI	Controls	Cases	OR3	95% CI	Controls	Cases	OR4	95% CI	Controls	Cases	OR5	95% CI
Missing	407	559	1.6	1.4–1.9	34	43	1.5	0.9–2.4	2	1	—		2	1	—		2	1	—	
Mother self-identified as Māori on Electoral Roll																				
No	2413	2281	1.0	Ref	916	861	1.0	Ref	457	576	1.0	Ref	457	576	1.0	Ref	457	576	1.0	Ref
Yes	576	429	0.8	0.7–0.9	103	130	1.3	1.0–1.8	48	76	1.3	0.9–1.8	48	76	1.1	0.7–1.6	48	76	0.8	0.6–1.1

and unweighted ORs based on the study participants only (OR3). These can be compared to the unweighted but adjusted ORs (OR4 in Table 1), and the weighted ORs (OR5 in Table 1).

The ORs based on the prerecruitment sample (OR1) are all close to 1, indicating that the four baseline characteristics were not associated with case–control status (under this scenario, not adjusted for any confounders, for all CA combined).

The estimates for OR2 (based on those that were contacted including the refusals), were elevated and reached statistical significance for the most deprived mothers, the youngest mothers, mothers not in paid employment, and those of Māori ethnicity, indicating that these demographic groups were more difficult to contact, particularly the controls, resulting in "contactability bias" related to all four baseline characteristics of the mother.

The estimates for OR3 represent the ORs when only study participants were included. This does not appear to further bias the ORs (OR3 vs. OR2), except for occupation of the mother, showing further inflation of the ORs for mothers in blue-collar occupations and not in paid employment (compared to white-collar occupations), which indicates that mothers in these occupational groups were more likely to refuse participation, particularly controls, resulting in "refusal bias" for the ORs related to occupation.

The estimates for OR4 represent the unweighted but adjusted ORs, which indicate that while some of the observed nonresponse bias (OR3) is removed through adjustment, this strategy is not as successful as inverse probability weighting. This is shown by the findings for OR5 that represent the ORs using the IPW. This shows ORs very similar to the crude ORs based on prerecruitment analyses (OR1), indicating that nonresponse bias in relation to the four baseline characteristics of the mother, is largely removed using the weights; wider confidence intervals can be observed for OR5 compared to OR1, but this is expected since numbers are smaller in some categories.

3.4 | Potential Impact of Nonresponse Bias on Risk Factor Prevalence and ORs

Table 2 presents the ORs for four selected CA risk factors that were collected via questionnaire and therefore only available for the participant population. These include smoking status, body mass index (BMI), highest education level achieved, and usual alcohol consumption (units per week). ORs are presented crude (i.e., not weighted or adjusted; OR1), adjusted for the 4 baseline characteristics (OR2), and weighted for the 4 baseline characteristics (OR3), with the difference between OR1 and OR3 considered indicative of nonresponse bias under the assumption that weighting removes nonresponse bias as illustrated in Table 1. Risk factor prevalence is also provided, to quantify how much the observed prevalence differs from the weighted prevalence, with the latter assumed to be indicative of the "true" prevalence.

Table 2 indicates that current smokers are underrepresented among participants, particularly among controls (crude prevalence 15%, weighted prevalence 24%), resulting in an inflated OR

TABLE 2 | Effect of weighting of the participant population toward the demographic distribution of the prerecruitment sample, on exposure prevalence and OR.

Characteristics collected via questionnaire	Unweighted						Weighted			
	Controls (%)	Cases (%)	Crude		Adjusted[a]		Controls (%)	Cases (%)	Crude	
			OR1	(95% CI)	OR2	(95% CI)			OR3	(95% CI)
Smoking status										
Never	63.1	53.8	1.0	(Reference)	1.0	(Reference)	56.9	50.2	1.0	(Reference)
Ex	21.8	22.8	1.2	(0.9, 1.7)	1.3	(1.0, 1.8)	18.8	21.9	1.3	(0.98, 1.8)
Current	15.1	23.4	1.8	(1.3, 2.5)	1.6	(1.1, 2.1)	24.3	27.9	1.3	(0.98,1.7)
BMI										
< 18.5	4.3	3.7	0.9	(0.5, 1.8)	0.9	(0.5, 1.7)	6.0	3.9	0.7	(0.4, 1.2)
18.5–25	58.4	52.8	1.0	(Reference)	1.0	(Reference)	52.9	51.1	1.0	(Reference)
25–30	22.6	24.1	1.2	(0.9, 1.6)	1.1	(0.8, 1.6)	23.5	24.4	1.1	(0.8, 1.5)
30–35	10.0	12.4	1.4	(0.9, 2.1)	1.3	(0.9, 2.0)	11.1	12.7	1.2	(0.8, 1.8)
35–40	2.8	3.0	1.2	(0.6, 2.5)	1.1	(0.5, 2.3)	4.0	3.0	0.8	(0.4, 1.5)
> 40	2.0	4.0	2.3	(1.0, 5.0)	2.0	(0.9, 4.5)	2.5	4.9	2.0	(1.0, 4.0)
Education (highest)										
Primary	0.6	1.3	2.5	(0.6, 9.5)	2.2	(0.6, 8.4)	1.6	1.2	0.8	(0.3, 2.3)
Secondary	23.1	35.6	1.9	(1.4, 2.4)	1.7	(1.3, 2.2)	30.6	37.2	1.3	(1.0, 1.7)
Tertiary	76.3	63.2	1.0	(Reference)	1.0	(Reference)	67.8	61.6	1.0	(Reference)
Alcohol (units per week)										
≤ 1	17.5	13.6	1.0	(Reference)	1.0	(Reference)	17.7	12.9	1.0	(Reference)
> 1–4	32.8	34.6	1.4	(0.9, 2.0)	1.4	(0.9, 2.1)	35.1	34.0	1.3	(0.9, 2.0)
> 4–10	32.4	31.8	1.3	(0.9, 1.9)	1.3	(0.9, 2.0)	29.8	31.6	1.5	(0.9, 2.2)
> 10	17.3	20.1	1.5	(1.0, 2.3)	1.5	(0.9, 2.3)	17.4	21.5	1.7	(1.1, 2.6)

Note: The ORs presented here are for the sole purpose of demonstrating the effects of nonresponse bias and inverse probability weighting. Study results on risk factors for CA will be reported elsewhere, for exposure variables specific to the index pregnancy, and adjusted for relevant confounders.
[a]Adjusted for variables in Table 1 (the weighting variables).

for current smoking (1.8 crude, 1.3 weighted). Prevalence of BMI outside the normal range is only slightly underestimated among the participants, and ORs did not change much after weighting. The prevalence of less than tertiary education was underestimated, particularly for controls (24% crude, 32% weighted), which resulted in inflated ORs (1.9 crude, 1.3 weighted for secondary compared to tertiary education). The prevalence of usually drinking > 10 units of alcohol per week was slightly underestimated among cases (20.1% crude, 21.5% weighted) resulting in a slight masking of the elevated OR (1.5 crude, 1.7 weighted).

The adjusted ORs were similar to the unadjusted ORs, suggesting that adjusting for the baseline characteristics was less effective in reducing nonresponse bias than weighting for baseline characteristics.

4 | Discussion

In this case–control study of modifiable risk factors of CA, we encountered several challenges. Those with implications for study interpretation and future case–control studies of CA are discussed later.

Case ascertainment can be a challenge for studies of CA (Tinker et al. 2015). We made use of NZCAR, which has the advantage of being the most complete CA register for NZ, but it does not routinely include pregnancy terminations or stillbirths. CA surveillance programs typically cannot achieve complete case ascertainment among terminated pregnancies, and the proportion of cases missed can be substantial for some defects such as spina bifida (Howards et al. 2015). In the National Birth Defects Prevention Study (NBDPS) conducted in the United States, completeness of ascertainment of terminations of pregnancy for fetal anomaly was 21% (Howards et al. 2015), and it was estimated that for spina bifida this may result in a biased association for pre-pregnancy obesity (Howards et al. 2015). As our study did not include pregnancy terminations or stillbirths, the impact of this on the ORs could not be quantified; however, a more recent analysis of NBDPS data suggests that some bias is likely for high mortality defects, but for most birth defects, livebirth bias was not substantial (Heinke et al. 2020). Despite these limitations,

these findings suggest that NZCAR can be used for future CA research in NZ, in a similar manner to, for example, the NBDPS that was established as an ongoing infrastructure for birth defect research and prevention (Dolk 2015).

Participant recruitment was a greater challenge than expected. We made use of participant recruitment methods successfully applied in previous NZ cancer case–control studies focusing on occupational exposures (Dryson et al. 2008; T Mannetje et al. 2008), using mailed invitations followed by telephone contact. However, establishing contact with mothers, particularly with the two-stage consent process via the GP for case mothers, and finding a suitable time for interview took more time than anticipated, likely due to the study population being relatively young (making it more difficult to establish contact).

Despite considerable effort, participation rates were lower than expected. Based on our previous cancer case–control studies we anticipated a 30% participation rate, but this was only achieved for the oldest age group and the lowest area-level deprivation group, with steep declines in participation rates for those at younger age and higher area-level deprivation. We observed steep age-gradients particularly in contact rates, with control contact rates of 50% in the oldest group, to only 10% in the youngest group (Figure 3). The reason is likely due to the contact method applied (invitation letters followed by telephone contact) being less suitable for younger age groups. Many potential case and control mothers did not respond to up to three mailed invitations and follow-up by telephone was only possible for ~25% of controls for whom a landline number could be identified. This suggests, unsurprisingly, that families with young children are a difficult demographic to recruit in this way, as they often move residence (reducing the ability to make contact through mailed invites) and increasingly rely on mobile phones. The additional stage of GP consent for case mothers added a layer of complexity; nonetheless, the overall contact rates were similar for case and control mothers.

By contrast, refusal rates differed substantially between case and control mothers: of those contacted, 32% of case mothers and 49% of control mothers refused to participate. Refusal was not associated with age or area-level deprivation (Figure 3). We did not formally evaluate reasons for refusal, but a frequently raised concern was lack of time. The higher refusal rates for control mothers is not unexpected, given that the focus of the study was on CA. In the NBDPS, the response rate for cases was 71% and 67% for controls (Cogswell et al. 2009), also suggesting that case mothers may be more motivated to participate (Cogswell et al. 2009).

Considering the relatively low participation rate, it was a strength that key characteristics of both participants and nonparticipants were available through linkage with the Electoral Roll. This allowed for a detailed evaluation of representativeness of the participants of the source population, for both cases and controls. IPWs were able to be developed and the impact of nonresponse bias on the risk estimates could therefore be quantified. This is generally not possible in most studies, where only aggregate data on characteristics of the source population are available. In this study, most nonresponse bias was introduced in the step of establishing contact, while refusal introduced relatively little additional bias. Thus, observed bias was therefore mostly 'contactability bias'. Only mother's occupation appeared to be susceptible to both "contactability bias" and "refusal bias" (Table 2). It is possible that the presence of potential occupational risk for CA in the workplace of the mothers (as occurs more often in blue-collar occupations) may have been an additional motivator to participate in the study, and that this has impacted more on case mothers than control mothers. As occupational risk factors are a significant focus of this study, this is of concern, although it is reassuring that IPW removed the false-positive association observed for blue- vs. white-collar workers (Table 1).

Adjustment for age and NZDEP removed some nonresponse bias, but this strategy was markedly less effective than IPW (Tables 1 and 2). Additionally, using adjustment will not remove any of the bias in exposure prevalence estimates resulting from the study. The results presented in Table 2 illustrate that this bias can be substantial, particularly among controls. For example, the observed smoking prevalence among controls was 15%, while the weighted prevalence, indicative of the "true" prevalence, was substantially higher at 24%, which was also reported in NZ by Tobias and Huang (2007). This may affect subsequent population attributable fraction (PAF) analyses, which assume that exposures among controls are representative for the general population (Cogswell et al. 2009). This study illustrated that IPW can provide more valid exposure prevalence estimates (in particular those that vary by age and area-level deprivation group), thus likely contributing to more accurate PAF estimates.

Retrospective exposure assessment through interview is susceptible to recall bias (Dolk 2015), which may lead to false-positive findings if case mothers are more likely to recall exposures than control mothers. In addition, the average lag time from birth to interview differed slightly between cases (3.8 years) and controls (4.7 years). While the possibility of recall bias can never be entirely eliminated, different strategies can be applied to evaluate whether this may have occurred. At analysis stage, results for certain exposures can be compared for different CA to find patterns that do not suggest recall bias. For example, folic acid supplementation can be expected to be associated with a reduced risk of neural tube defects but generally not other CAs. Recall bias can be eliminated entirely by using objective exposure data from other sources, such as, for example, linked routinely collected pharmaceutical data or occupation data from birth records, and additional studies using this strategy will be able to validate findings of studies susceptible to recall bias. Future analyses from this study will also be adjusted for time between birth and interview.

In this study, multiple CAs were included, which has the advantage that risk estimates can be compared between CAs, but the disadvantage is that study power is low for CA groups and too low for most individual CA. This limitation can be addressed in future case–control studies focusing on specific CAs, as well as through data linkage studies focusing on specific risk factors that are routinely collected such as pharmaceutical prescriptions.

5 | Conclusions

This NZ case–control study into modifiable risk factors for CA encountered several challenges related to relatively low

participation rates. IPWs were found to be effective in removing the observed nonresponse bias, and these will be applied in ongoing data analyses. Also, further linkage studies will be developed to address other limitations discussed above.

Author Contributions

A.M., A.E., L.E.-L., B.B., J.D., and N.P. made substantial contributions to the study design. B.B. and J.D. arranged access to data. A.M., A.E., D.A.L., J.D., and N.P. made substantial contributions to the interpretation of data. A.M. and A.E. produced the first draft of the manuscript. A.M., A.E., L.E.-L., B.B., J.D., and N.P. contributed to critical manuscript revision. All authors contributed and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ethics Statement

Ethical approval was obtained from the NZ Multi-region Ethics Committee (MEC/07/08/113).

Consent

All participants provided written informed consent.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Research data are not shared.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.