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Childhood asthma and smoking exposures before conception – a three-generational cohort study.

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Abstract

Background: Some human and animal studies have recently shown that maternal grandmother's smoking during pregnancy increases the risk of asthma in the grandchildren. We have investigated whether sex of the exposed parent and/or grandchild modifies the association between grandmaternal smoking and grandchild asthma.

Methods: We formed a cohort study based on linkage of national registries with prospectively collected data over three generations. Smoking habits in early pregnancy were registered since 1982 and purchases of prescribed medication since 2005. In all, 10329 children born since 2005 had information on maternal and grandmaternal smoking on both sides and were followed from birth up to 6 years of age. Ages when medication was purchased were used to classify the cohort into never, early transient (0-3 years), early persistent (0-3 and 4-6 years) and late-onset (4-6 years) phenotypes of childhood asthma.
Results: Maternal grandmother's smoking was associated with an increased odds of early persistent asthma after adjustment for maternal smoking and other confounders (odds ratio 1.29, 95% confidence interval 1.10-1.51). Grandchild sex did not modify the association. Paternal grandmother's smoking was not associated with any of the asthma phenotypes.
Conclusion: Maternal but not paternal exposure to nicotine before conception was related to

an increased risk of early persistent childhood asthma, but not other asthma phenotypes. Our findings are possibly consistent with a sex specific mode of epigenetic transfer.

Key words childhood asthma, grandmother, pregnancy, tobacco smoke, multigenerational study

INTRODUCTION

Asthma is caused by a complex interaction between genes and environment. Epigenetic alterations caused by environmental factors are heritable and affect the expression of genes without changing the sequence of DNA (1). Nicotine is a potent inducer of epigenetic changes in the human fetus (2) and epigenetic information may pass across the generations via the germ-line (3). There is some evidence from a limited number of studies that smoke exposure before conception is related to an increased risk of asthma in the subsequent generations (4). Animal studies have demonstrated that nicotine exposure during pregnancy causes pulmonary effects in the non-exposed grand-offspring (5, 6) and this is related to epigenetic alterations in the fetal germ cells (6). Exposure effects could be sex dependent (7, 8) and there is increasing interest in understanding whether epigenetic intergenerational transmission differs between the male and the female germ lines (9). Human studies published so far have focused on the risk of grandchild asthma related to maternal grandmother´s smoking. Two studies demonstrated an increased risk of grandchild asthma independent of maternal smoking (10, 11) whereas one failed to find any association between maternal grandmother's smoking and the risk of asthma at 7 years (12). In contrast, paternal prenatal exposure to tobacco smoke was associated with an increased risk of asthma but only in the granddaughters (12).

Decreasing response rates together with selection and recall bias is often problematic in three-generational studies built on retrospective reporting, but many of these problems can be addressed in registry-based surveys (13). National registries covering all Swedish inhabitants have enabled us to set up cohorts with prospectively collected data over three generations. We have recently demonstrated that maternal grandmother´s smoking in early pregnancy was associated with an increased risk of asthma in the first six years of life and the increased risk persisted even in children with non-smoking mothers (14). The aim of the current study was

to assess whether sex of the exposed parent and/or grandchild modified the association between grandmaternal smoking and offspring asthma.

METHODS

This study is based on record linkage of Swedish national registries at an individual level. All women who gave birth to a child between 1982 and 1986 and their children were identified from the Medical Birth Register. The grandchildren and the fathers of the children and the grandchildren were identified from the Multi-Generation Register. The study cohort included only those, where we had full information on smoking habits in early pregnancy for mothers as well as maternal and paternal grandmothers. Further details of the study population in Fig 1 and in supporting information online. The study was approved by the Regional Ethic Review Board in Umeå, Sweden.

Exposure classification

Maternal smoking habits in early pregnancy (0,1-9 or more than 9 cigarettes per day) have been registered in the Medical Birth Register all over the country since 1982. It is based on a personal interview by a skilled midwife when a pregnant woman has her first visit to the maternity clinic (usually in week 8-12). Registration of maternal smoking habits is missing for less than 8% among those born after 1982.

Primary outcome

The Swedish Prescribed Drug Register contains all dispensed and prescribed medicines since 1 July 2005. We have used dispensed prescriptions of a leukotriene antagonist (Anatomic Therapeutic Chemical (ATC) code R03DC03) or an inhaled corticosteroid (ATC codes R03AK06, R03AK07, R03AK08, R03AK11, R03BA) as a proxy for asthma. We have defined three phenotypes of asthma during the first six years of life consistent with a classification suggested by Martinez et al (15):

Early persistent asthma: purchase of at least two prescriptions of asthma medication before three years of age and at least two purchases after three years of age

Early transient asthma: purchase of at least two prescriptions of asthma medication before three years of age and no purchases after three years of age

Late-onset asthma: purchase of at least two prescriptions of asthma medication after three years of age but no purchases before three years of age.

We tested two models. One model was restricted to purchase of prescribed inhaled corticosteroids and/or leukotriene antagonists. The other model included purchase of any asthma medication (comprising also inhaled beta-agonists, R03AC and R03AL).

Secondary outcome

The Swedish Patient Register comprises in-patient and out-patient hospital care all over the country. We have used any hospital care for asthma as a secondary outcome.

Educational level

The Swedish Educational Register contains information on the highest educational level (number of years at school) for every resident in Sweden aged 16-74 years.

Social assistance

Cash income allowance to the household, calculated by local social authorities. Data was obtained from the Social Assistance Register.

Statistics

Multinomial logistic regression was used to estimate potential associations between smoking habits during pregnancy and asthma phenotype, and separate logistic regression models were used for each year of asthma medication in the child or grandchild. Family clustering was not taken into consideration,

because each grandmother had so few grandchildren (on average 1.19 grandchildren per maternal grandmother and 1.23 grandchildren per paternal grandmother). The models were developed in three steps; in the first step unadjusted models were fitted, in the second step the models were simultaneously adjusted for smoking habits during both the grandmothers pregnancies and the mothers pregnancy, and in the third step the models were adjusted for educational level, social assistance, age at pregnancy (grand maternal, maternal and paternal), grandmaternal BMI in early pregnancy, grandparental asthma medication, sex of the child, and county of residence at mothers and fathers birth. 95 % confidence intervals (CI) were implemented to assess statistical significance. Additionally we analyzed if any association between smoking during pregnancy and childhood asthma was modified by birth weight (2nd or 3rd generation), parental asthma, maternal BMI or parental level of education. Each potential modifier was entered into the fully adjusted model separately, and we studied changes in the estimated odds ratio.

RESULTS

In all, 42% of the grandmothers were smoking in early pregnancy as compared with 16% of the mothers. Mean age at child birth among grandmothers, mothers and fathers was 26 years, 22.8 years and 23.4 years, respectively. Corresponding rate of grandmothers, mothers and fathers with less than 12 years at school was 68%, 23% and 27%. At child birth, 9.6% of the mothers (1004/10371) were not living together with the father of the child and information concerning habitation was missing for another 70 mothers. During the first six years of life, 17.8 % of the children had at least one purchase of inhaled corticosteroids or leukotriene antagonists and 15.7% had been diagnosed with asthma by a hospital doctor (Table 1). The birth weight was reduced in children who had been exposed to maternal smoking in utero (Table S1).

Paternal grandmother's smoking had no relationship with asthma medication (Table 2), any asthma phenotype (Table 3 and 4) or hospital care for asthma (Table 5). In contrast, maternal grandmother's smoking was associated with increased odds ratios (OR) of asthma medication (Table 2), hospital care for asthma (Table 5) and early persistent asthma (Table 3 and 4) but the associations were not always significant and the associations between maternal grandmother's smoking and child asthma medication were not dose-dependent. Maternal grandmother's smoking was associated with an increased odds of

early persistent asthma in both girls (adjusted OR 1.45, 95% CI 1.13-1.87) and boys (adjusted OR 1.21, 95% CI 0.98-1.48), but the association was only significant in girls (p for interaction =0.28). Other potential modifiers had negligible effects on the ORs. The increased odds for grandchild asthma related to maternal grandmother's smoking in pregnancy remained consistent after exclusion of children whose mothers were single at child birth (Table S2 and S3).

Maternal smoking was associated with increased risk of hospital care for asthma during the first two years of life (Table 5). It was also associated with an increased risk of transient asthma when asthma was defined using any asthma medication (Table 4). No association was observed when the definition of asthma phenotype was restricted to prescribed corticosteroids and/or leukotriene antagonists (Table 3).

DISCUSSION

This three-generational registry-based cohort study with grandchildren followed up to six years of age has several important strengths in comparison with previous studies. All data on exposures as well as outcome were collected prospectively. Attrition rate was negligible and the analyses were not limited by recall or selection bias. Maternal grandmother's smoking in early pregnancy was associated with an increased risk of early persistent asthma even in grandchildren with mothers who did not smoke during pregnancy. In contrast, paternal grandmothers smoking did not affect the risk of grandchild asthma.

The increased risk of grandchild asthma related to grandmaternal smoking was transmitted through the maternal line and was independent of maternal smoking during pregnancy and paternal grandmother's smoking habits. Grandchild asthma could be due to a direct effect on the female germ cells caused by grandmother's smoking during pregnancy (16) but an effect could also be indirect through mediating factors along the pathway over the generations and intra-uterine exposures are particularly important (17). We had information on birth weight and some other potential mediators from the registers. Although we have not done a formal

mediation analysis, adjustment for these factors had no or negligible effect on the association between grandmaternal smoking and grandchild asthma.

The offspring inherit not only the genes but also social position, attitudes and life style pattern from parents and grandparents. Recent studies have demonstrated that grandmaternal educational level (18), poverty (19) and socioeconomic position (20) affect birth weight, health status and obesity in the grandchildren and the effects are partly independent of schooling and income in the intermediate generation. We have used parental education level as a marker of socioeconomic status and achieved social welfare as a marker of poverty. We had access to a range of factors that could plausibly confound these associations, yet the increased risk of grandchild asthma related to maternal grandmother's smoking persisted after adjustment for these factors. Given the observational nature of this study, it remains possible that the results could be due to residual confounding. The mother is still the main caregiver in Sweden and particularly so during the first year of life. Mothers take three quarters of all parental leave. Mothers as compared with mothers-in-law are more likely to be role models for their daughters (21, 22). Even if they do not smoke they may have adopted dietary habits or other life style patterns from their mothers, which affect the association between maternal grandmother's smoking and offspring asthma.

It is possible that the increased risk of grandchild asthma is from postnatal exposure of the grandchild to grandmother's smoking as the grandmother may provide childcare especially if the mother is working. However, our sensitivity analysis that excluded single mothers, the group most likely to receive grandmothers' support, did not materially change our findings. Moreover, considering that grandmaternal child support is likely to happen more than 20 years after their pregnancy smoking habits were recorded, along with the change in societal smoking norms, there is likely to have been a reduction in grandmaternal smoking practices, including exposing young children to second-hand smoke. There is an increased awareness that exposure to indoor smoking may be harmful for children and smoking indoors is banned in most Swedish public institutions. In all, 42% of the grandmothers smoked during pregnancy in the 1980s whereas only 20% of all women aged 45-64 years were daily smokers in 2010 (23). In addition, the time grandparents spend with the grandchildren is limited in

countries like Sweden with strong welfare arrangements (22). Swedish parents are entitled 480 days of paid parental leave and most children start preschool during the second year of life.

Maternal smoking during pregnancy leads to reduced birth weight and the effect is dose-dependent. No effect is observed when the mothers stop smoking in early pregnancy (24). Similarly, DNA methylation changes in the newborn children are related to the length of in-utero nicotine exposure (2). In our study, the mean birth weight for girls in the second generation exposed to maternal smoking in early fetal life was more than 200g lower than for those born to nonsmoking mothers. However, the difference in birthweight related to smoking more or less than 10 cigarettes per day was insignificant suggesting that maternal smoking habits had changed after the first trimester. This is likely to explain why we did not detect any difference in grandchild asthma risk related to number of cigarettes smoked per day in early pregnancy by the grandmothers.

A diagnosis of asthma is often uncertain in very young children (25). We have used prescribed asthma medication as a proxy for asthma. In Sweden, an inhaled beta-agonist may be prescribed as single therapy for children with mild, viral induced wheeze whereas inhaled corticosteroids and/or leukotriene antagonists are added for children with recurrent wheeze and/or concomitant symptoms of atopy. We investigated two classifications of asthma. One model was restricted to inhaled corticosteroids and/ or leukotriene antagonists. The other model based on any asthma medication was likely to include also children with mild symptoms. Maternal grandmother's smoking was a risk factor for early persistent asthma in both models. In contrast, maternal smoking was associated with an increased risk for transient asthma but only in the model based on any asthma medication. Declining smoking habits over the generations may have reduced the power to detect the association between maternal smoking and offspring asthma.

Increasing or unchanged prevalence of childhood asthma despite declining smoking habits is a paradox. However, the cumulative risk from smoking exposure in previous generations has resulted in a delayed increase in asthma risk for subsequent generations even though smoking rates are falling.

There is no information concerning paternal smoking habits in the registers. In men, primordial germ cells are differentiated to mature spermatocytes in early puberty and this is a critical time window with an increased susceptibility to epigenetic alterations caused by harmful external exposures (26). A recent study demonstrated an increased risk of non-allergic asthma in individuals whose fathers had started to smoke in early puberty. However, the increased risk of childhood asthma was only observed in fathers with nonsmoking mothers (27). Therefore, we cannot exclude that a potential association between paternal grandmothers smoking and grandchild asthma has been modified and diluted by paternal smoking in early puberty. Smoking among the fathers in our cohort is likely to be common. They were young and 27% had less than 12 years schooling as compared with 16% among Swedish-born men in a corresponding age group in Sweden in 2006 (28).

To conclude, maternal but not paternal exposure to nicotine before conception was related to an increased risk of early persistent childhood asthma, but not other asthma phenotypes. Our findings are possibly consistent with a sex specific mode of epigenetic transfer. Maternal grandmother's smoking during pregnancy appeared to be a stronger risk factor for childhood asthma and associated with a different asthma phenotype than corresponding smoking by the mother.

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Conflict of interest

The authors declare that they have no conflict of interest

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Figure legend

Fig. 1. Study population

Supporting information

Additional Supporting Information may be found online in the supporting information tab to this article

TABLE 1. Child's clinical and demographic characteristics up to six years of age.

		included	excluded[a]	p-value
Number of subjects		10329	4575	
Gender	male	51.50%	52.61%	0.21
	female	48.50%	47.39%	
First child		73.93%	70.84%	<0.001
Purchased asthma medication (any)		20.99%	22.47%	0.04
Purchased asthma medication (inhaled steroid and/or leukotriene antagonist)		17.75%	18.93%	0.09
Asthma (Inpatient or outpatient hospital care)		15.71%	17.14%	0.03
Any asthma medication by year of life	Year1	1.69%	1.77%	0.73
	Year2	8.25%	9.33%	0.03
	Year3	11.37%	11.89%	0.36
	Year4	10.19%	11.10%	0.10
	Year5	8.71%	9.71%	0.05
	Year6	7.99%	8.33%	0.48
Any inhaled steroid and/or leukotriene antagonist) by year of life	Year1	1.21%	1.33%	0.55
	Year2	6.64%	7.59%	0.04
	Year3	9.65%	10.12%	0.37
	Year4	8.64%	9.44%	0.12
	Year5	7.40%	8.26%	0.07
	Year6	6.69%	6.93%	0.59

[a] No information on grandmaternal smoking in the Medical Birth Register (most of these children were born during the first half of 1982).

TABLE 2. Odds ratios (95% confidence interval) of annual purchase of inhaled steroid and/or leukotriene antagonist (at least one prescription) in relation to maternal and grandmaternal smoking smoking habits (no smoking/1-9 cigarettes per day/10 cigarettes or more per day) in early pregnancy (N=10329) [a]

	Paternal grandmother		Maternal grandmother		Mother	
	1-9 cig/day	≥10 cig/day	1-9 cig/day	≥10 cig/day	1-9 cig/day	≥10 cig/day
1st year	1.11 (0.71-1.72)	0.89 (0.53-1.52)	0.91 (0.58- 1.44)	1.05 (0.63-1.72)	1.40 (0.84-2.34)	1.53 (0.59 - 3.96)
2nd year	1.02 (0.84-1.24)	0.87 (0.69 -1.09)	1.35 (1.12- 1.63)	1.17 (0.93-1.46)	1.18 (0.94-1.49)	1.46 (0.95 - 2.26)
3rd year	1.06 (0.90- 1.25)	0.94 (0.78-1.14)	1.17 (1.00- 1.38)	1.13 (0.94- 1.36)	1.05 (0.85-1.28)	1.20 (0.81 - 1.78)
4th year	1.02 (0.86- 1.21)	0.83 (0.68-1.02)	1.25 (1.06- 1.48)	1.21 (1.00- 1.47)	1.07 (0.86-1.32)	1.00 (0.65 - 1.55)
5th year	1.02 (0.85- 1.23)	0.85 (0.68-1.06)	1.14 (0.95- 1.37)	1.24 (1.01- 1.52)	0.84 (0.66-1.08)	0.91 (0.57 - 1.47
6th year	0.93 (0.76- 1.13)	0.78 (0.62-0.98)	1.17 (0.97 1.42)	1.15 (0.93- 1.43)	1.03 (0.81-1.31)	1.04 (0.64 - 1.70)

[a] 0 cigarettes per day is the reference group for all analyses. Associations are mutual adjusted for maternal and grandmaternal smoking habits and also adjusted for maternal and paternal grandmothers age, level of education, social welfare, body mass index and asthma medication, sex of the grandchild, and county of residence at mother's and father's birth

TABLE 3. Asthma phenotypes in grandchildren by grandmaternal and maternal smoking (at least one cig per day) in early pregnancy. Asthma phenotypes definitions based on prescriptions of inhaled steroids and/or leukotriene antagonists.

Smoking status	Early transient asthma OR (95% CI)[d]	Early persistent asthma OR (95% CI) [d]	Late-onset asthma OR (95% CI) [d]
Model A[a]			
N	272	440	360
Paternal grandmother smoking	1.06 (0.83 - 1.36)	1.05 (0.86 - 1.27)	0.87 (0.70 - 1.08)
Maternal grandmother smoking	0.84 (0.66 - 1.08)	1.31 (1.09 - 1.59)	0.98 (0.79 - 1.21)
Maternal smoking	1.13 (0.82 - 1.55)	1.24 (0.97 - 1.58)	0.95 (0.71 - 1.28)
Model B[b]			
N	272	440	360
Paternal grandmother smoking	1.06 (0.83 - 1.36)	1.01 (0.83 - 1.23)	0.87 (0.70 - 1.08)
Maternal grandmother smoking	0.81 (0.63 - 1.05)	1.28 (1.05 - 1.56)	0.99 (0.80 - 1.23)
Maternal smoking	1.18 (0.85 - 1.64)	1.15 (0.89 - 1.48)	0.98 (0.72 - 1.32)
Model C[c]			
N	265	423	343
Paternal grandmother smoking	1.12 (0.86 - 1.45)	0.96 (0.78 - 1.18)	0.87 (0.69 - 1.10)
Maternal grandmother smoking	0.82 (0.62 - 1.06)	1.28 (1.04 - 1.58)	1.01 (0.80 - 1.27)
Maternal smoking	1.16 (0.82 - 1.64)	1.15 (0.88 - 1.51)	0.98 (0.71 - 1.35)

OR odds ratios

[a] Model A: Crude OR

[b] Model B: ORs after mutual adjustment for grandmaternal and maternal smoking habits

[c] Model C: ORs also adjusted for maternal and paternal grandmothers age, level of education, social welfare, body mass index and asthma medication, sex of the grandchild, and county of residence at mother's and father's birth

[d] Estimates of associations from multinomial logistic regression model where the reference group for all analyses are those with no asthma/wheeze (defined as less than two purchases of inhaled steroids

and/or leukotriene antagonists before three years of age and less than two purchases of inhaled steroids and/or leukotriene antagonists after three years).

TABLE 4. Asthma phenotypes in grandchildren by grandmaternal and maternal smoking (at least one cig per day) in early pregnancy. Asthma phenotypes definitions based on prescriptions of any asthma medication (including also beta-agonists).

Smoking status	Early transient asthma OR (95% CI)[d]	Early persistent asthma OR (95% CI) [d]	Late-onset asthma OR (95% CI) [d]
Model A[a]			
N	442	764	510
Paternal grandmother smoking	1.12 (0.93 - 1.36)	1.00 (0.86 - 1.17)	0.92 (0.76 - 1.10)
Maternal grandmother smoking	1.04 (0.86 - 1.26)	1.32 (1.14 - 1.53)	0.98 (0.82 - 1.17)
Maternal smoking	1.39 (1.10 - 1.77)	1.29 (1.06 - 1.55)	1.01 (0.79 - 1.30)
Model B[b]			
N	442	764	510
Paternal grandmother smoking	1.09 (0.90 - 1.32)	0.97 (0.83 - 1.13)	0.92 (0.76 - 1.10)
Maternal grandmother smoking	0.98 (0.80 - 1.20)	1.29 (1.10 - 1.50)	0.98 (0.82 - 1.18)
Maternal smoking	1.38 (1.08 - 1.77)	1.20 (0.99 - 1.47)	1.03 (0.80 - 1.33)
Model C[c]			
N	425	728	486
Paternal grandmother smoking	1.10 (0.90 - 1.36)	0.93 (0.79 - 1.09)	0.91 (0.75 - 1.11)
Maternal grandmother smoking	0.99 (0.80 - 1.22)	1.27 (1.08 - 1.49)	0.97 (0.80 - 1.19)

Maternal smoking	1.30 (1.00 - 1.70)	1.17 (0.94 - 1.44)	1.00 (0.76 - 1.31)

OR odds ratios

[a] Model A: Crude OR

[b] Model B: ORs after mutual adjustment for grandmaternal and maternal smoking habits

[c] Model C: ORs also adjusted for maternal and paternal grandmothers age, level of education, social welfare, body mass index and asthma medication, sex of the grandchild, and county of residence at mother's and father's birth

[d] Estimates of associations from multinomial logistic regression model where the reference group for all analyses are those with no asthma/wheeze (defined as less than two purchases of any asthma medication during the first six years of life).

TABLE 5. Hospital care for asthma during the first six years of life in relation to grandmaternal and maternal smoking habits during pregnancy (PGM=Paternal grandmother's smoking, MGM=Maternal grandmother's smoking, M=Maternal smoking). Smoking defined as at least one cigarette per day.

Model A. Unadjusted odds ratios (N=10690)

	PGM	MGM	M	Cases
1st year	0.95 (0.75 - 1.20)	1.30 (1.03 - 1.64)	1.59 (1.20 - 2.09)	296
2nd year	1.06 (0.90 - 1.24)	1.31 (1.12 - 1.53)	1.44 (1.19 - 1.75)	682o
3rd year	1.02 (0.87 - 1.19)	1.19 (1.02 - 1.38)	1.26 (1.04 - 1.53)	727
4th year	1.00 (0.85 - 1.19)	1.25 (1.06 - 1.47)	1.15 (0.92 - 1.43)	592
5th year	0.96 (0.80 - 1.15)	1.17 (0.98 - 1.40)	0.88 (0.68 - 1.13)	514
6th year	0.94 (0.77 - 1.15)	1.31 (1.08 - 1.59)	1.03 (0.79 - 1.34)	415

Model B. Mutually adjusted for grandparental and maternal smoking during pregnancy (N=10690)

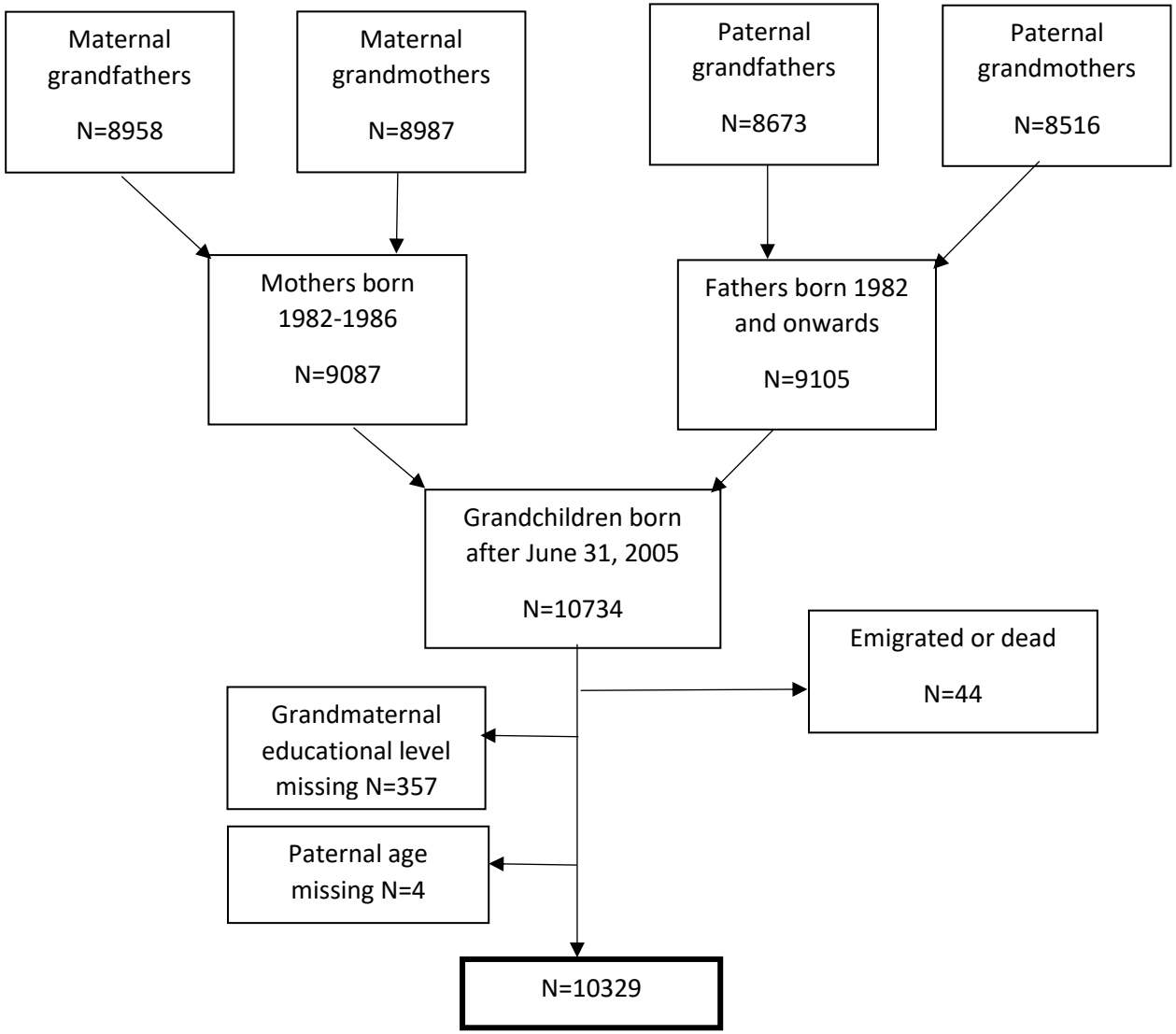
	PGM	MGM	M	Cases
1st year	0.89 (0.70 - 1.13)	1.22 (0.96 - 1.55)	1.53 (1.15 - 2.04)	296
2nd year	1.01 (0.86 - 1.18)	1.25 (1.06 - 1.46)	1.35 (1.11 - 1.65)	682

3rd year	0.99 (0.85 - 1.15)	1.15 (0.99 - 1.34)	1.21 (0.99 - 1.48)	727
4th year	0.98 (0.83 - 1.16)	1.23 (1.04 - 1.46)	1.09 (0.87 - 1.36)	592
5th year	0.97 (0.80 - 1.16)	1.21 (1.01 - 1.45)	0.84 (0.65 - 1.09)	514
6th year	0.93 (0.76 - 1.13)	1.32 (1.08 - 1.62)	0.96 (0.73 - 1.27)	415

Model C. ORs also adjusted for maternal and paternal grandmothers age, level of education, social welfare, body mass index and asthma medication, sex of the grandchild, and county of residence at mother's and father's birth (N=10329).

	PGM	MGM	M	Cases
1st year	0.87 (0.67 - 1.13)	1.24 (0.96 - 1.59)	1.35 (0.98 - 1.85)	283
2nd year	0.97 (0.82 - 1.15)	1.22 (1.03 - 1.44)	1.25 (1.00 - 1.55)	649
3rd year	0.96 (0.82 - 1.13)	1.11 (0.94 - 1.31)	1.13 (0.91 - 1.41)	691
4th year	0.95 (0.79 - 1.14)	1.19 (0.99 - 1.42)	1.05 (0.82 - 1.34)	563
5th year	0.93 (0.77 - 1.13)	1.21 (0.99 - 1.46)	0.79 (0.60 - 1.05)	489
6th year	0.91 (0.73 - 1.13)	1.26 (1.02 - 1.56)	0.92 (0.68 - 1.23)	398

Fig. 1



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