Father’s environment before conception and asthma risk in his children: A multi-generation analysis of the Respiratory Health in Northern Europe study

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Background: While it is generally accepted that maternal environment plays a key role in child health, emerging evidence suggests that paternal environment before conception also impacts child health. We aimed to investigate the association between children’s asthma risk and parental smoking and welding exposures prior to conception.

Methods: In a longitudinal, multi-country study, parents of 24,168 offspring aged two to 51 years provided information on their life-course smoking habits, occupational exposure to welding and metal fumes, and offspring’s asthma before/after age ten years and hay fever. Logistic regressions investigated the relevant associations controlled for age, study centre, parental characteristics (age, asthma, education), and clustering by family.

Results: Non-allergic early-onset asthma (asthma without hayfever, present in 5.8%) was more common in the offspring with fathers who smoked before conception (OR=1.68 [95%CI=1.18-2.41]), while mother’s smoking before conception did not predict offspring asthma. The risk was highest if father started smoking before age 15 (3.24 [1.67-6.27]), even if he stopped more than five years before conception (2.68[1.17-6.13]). Father’s pre-conception welding was independently associated with non-allergic asthma in his offspring (1.80[1.29-2.50]). There was no effect if the father started welding or smoking after birth. The associations were consistent across countries.

Conclusions: Environmental exposures in young men appear to influence the respiratory health of their offspring born many years later. Influences during susceptible stages of spermatocyte development might be important and needs further investigation in humans. We hypothesise that protecting young men from harmful exposures may lead to improved respiratory health in future generations.

Key words: Asthma, Epidemiology, Smoking, Occupational Exposure, Epigenesis
Key messages:

- Smoking and occupational welding in young men appeared to independently increase asthma risk in their offspring born many years later.

- Early puberty might possibly be a critical vulnerable period.

- The findings provide an unexpectedly strong argument for focusing on the adverse environmental exposures of adolescent males.
INTRODUCTION

It is well known that a mother’s environment plays a key role in child health. The hypothesis that health and disease originate early in life, has dramatically increased our understanding of this issue and is guiding public health policy. However, emerging evidence suggests that there are mechanisms whereby the father’s environment before conception could also impact the health of future generations.¹

Environmental factors such as smoking and occupational exposures can cause genetic and epigenetic changes in sperm that are transmissible to offspring.²⁻⁹ There is evidence for inheritable effects of food restriction through the male line from human studies, suggesting particular effects on offspring when exposure occurs during prepuberty.¹⁰⁻¹³ The recent development of hypotheses regarding “windows of susceptibility” to environmental insults during sperm development suggests an urgent need to investigate exposures occurring in adolescent men with potential impacts for their offspring.² Such investigation requires large, long-term, epidemiologic studies of multiple generations.

One outcome where paternal exposures might play an important role is childhood asthma. Despite major scientific efforts and mounting evidence that asthma aetiology starts as early as the intra-uterine period, knowledge of the causal factors remains incomplete. There is some evidence that paternal in utero exposure to cigarette smoke is associated with his children’s asthma,¹⁴ but to our knowledge there are no studies of asthma investigating father’s exposures beyond this, including exposures prior to starting a family. Existing knowledge of inheritable spermatogenic effects make this an appealing target for investigating windows of susceptibility in fathers. In addition, occupational environmental exposures in young men prior to reproduction need to be investigated as the workplace provides an important source of potentially harmful exposures.²
The Respiratory Health In Northern Europe (RHINE) study provides a unique data set including detailed information on smoking habits and occupational exposure to welding and metal fumes from large population-based cohorts in multiple centres and countries, followed over a 20-year period. RHINE thus provides a rare opportunity for detailed investigation of parental environmental exposures and potential impact on asthma risk in their children. The most recent follow-up included information on asthma prevalence in participants’ offspring (27,120). Welding is a relevant occupational exposure implicated in a variety of respiratory health problems. It has also been shown to have effects on sperm quality.\textsuperscript{15-17}

In this study, we first aimed to investigate whether parental exposure to smoking and welding, including exposure prior to conception, influenced asthma risk in offspring, with a particular focus on exposures in fathers. Second, we aimed to identify susceptible windows during male reproductive development by addressing whether potential preconception effects were related to exposure age, exposure duration, and time from quitting exposure until conception.
METHODS

Study population

RHINE III is the second follow-up of a population-based cohort from seven Northern European centres (supplementary figure 1). Random population samples of men and women born 1945-73 completed postal questionnaires in 1991-93, 1999-2001 and 2010-12. In 2010-12, participants were asked about their children, including each child’s birth year, asthma, and allergies. The parent study (ECRHS) recruited random samples from population based registers in each country. The intention of this sampling was to recruit a population-based sample but not ‘families’ or ‘married/cohabiting couples’. Therefore we have information on women who became mothers, and men who became fathers – but not ‘couples who became parents. Thus, preconception information was available only for one of the offspring’s parents, the one that did participate in the parent study”. 1880 reported having no children, the remaining participants reported a total of 27120 children aged 0-51 years (mean age 22 years), with mean family size 1.9 siblings.

The studies were approved by medical research ethics regional committees according to national legislations. All participants gave written informed consent.

Parental smoking

RHINE participants provided information about smoking habits, including year of smoking debut and quitting. Parental smoking exposure was defined in three groups by relating this information to birth year for each offspring: 1)“Smoking only prior to conception”: parent quit smoking ≥ two years prior to child’s birth year; 2)“Smoking including period around birth”: parent smoked in the period around child’s birth; most smoked before, during and after pregnancy; 3)“Smoking started after birth”. Father’s age of starting smoking was categorised
as before or after 15 years, the mean age of completed puberty (mean age of voice break 14.5 years, first nocturnal emission 14.8 years).19

**Parental welding**

In the first follow-up (1999-2001), prior to collecting information about offspring (2010-11), parents were asked about occupational exposure to welding or metal fumes (‘Have you worked with welding or in any other way in your work been exposed to metal fumes/welding fumes?’). Those answering “yes” were asked about years of starting and quitting. Median age for starting welding was 19 years (interquartile range 17-22) among those who started welding before conception.

**Asthma phenotypes in offspring**

Asthma was defined based on the following question: “Please write the years when your children were born, and tick “YES” if they have had any of the following: Asthma before 10 year; Asthma after 10 years; Hayfever/rhinitis; Atopic eczema/skin allergies”. Asthma before ten years defined “early-onset asthma” and asthma after age ten years defined “later-onset asthma”. “Allergic asthma” was defined by a positive answer to asthma and to hayfever; “non-allergic asthma” as having asthma but not hayfever. Age 10 was set as cut-point to separate childhood asthma from asthma with onset in early puberty or later in both sexes.

Infants under two years of age were excluded from analyses as asthma diagnosis in this age group is unclear (n=175 excluded, two with parent-reported asthma).

**Statistical analysis**

Associations of parental smoking patterns and occupational welding with asthma phenotypes in offspring were analysed using logistic regressions adjusting for age, study centre and
parental characteristics (age, parent asthma before age ten, education level), and clustering by family using multilevel modelling. Analyses of welding included adjustment for smoking. Grandparent education, number of siblings and type of dwelling were considered as potential confounders in all analyses, but were not included in the final models as they did not alter the effect estimates by ≥5%.

Analyses were structured as follows:

1) We examined the association between maternal and paternal smoking during different periods (smoked only prior to conception; smoked including period around birth; smoked only after child’s birth) and asthma phenotypes (early onset and later onset asthma, further characterised as allergic and non-allergic asthma).

2) For the time periods and phenotypes where there was evidence of an association between smoking and asthma, we next tested for dose-response effects by examining age of smoking debut, smoking duration, amount and years before birth that smoking stopped.

3) Finally, we investigated whether the association between paternal smoking and asthma in offspring differed according to paternal grandmother’s smoking status (a marker of father’s in utero smoking exposure). For this analysis we created five mutually exclusive groups of paternal smoking: never smoked; smoking debut before age 15; smoking debut after age 15 and duration less than ten years before conception; smoking debut after age 15 and duration more than ten years before conception; smoking debut after conception.

The relationship between paternal welding (including age started and duration) with offspring asthma was analysed using similar definitions as for smoking (welding before or after age 15,
and for less or more than ten years). Only 40 fathers started welding before age 15; early onset welding was thus not analysed. Welding in mothers was uncommon and not analysed.

Meta analysis was conducted using both fixed effects and random effects models. Given there was almost no heterogeneity and both models gave identical results, we have presented the fixed effect models in the manuscript.

Sensitivity analyses were conducted to consider the effect of missing data and differential recall based on child’s reported asthma status (online supplementary material).

Stata Statistical Software was used to analyse the data (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).
RESULTS

Characteristics of the cohort

Of 26945 offspring over two years old, asthma status was reported for 24168 (90%); these were included in the analyses (supplementary table 1). Early- and later-onset asthma were present in 8.5% (allergic 2.6%; non-allergic 5.8%) and 4.2%, respectively (supplementary Table 1). Supplementary table 2a describes characteristics and outcomes by parental smoking history (never smoked 48%, smoked only prior to conception 10%, other smoking patterns 40%, smoked only after birth of child 1.6%). Supplementary table 2b describes characteristics and outcomes by paternal welding (never welded 79%, welded prior to conception 18%, welded only after birth of child 4%).

Relationship between paternal smoking and offspring asthma phenotypes

Individuals with a father who smoked only prior to conception had more early-onset asthma than those whose father never smoked (table 1). This was due to an association with non-allergic early-onset asthma. There was no association with late onset asthma (table 1), including when late onset asthma was further divided into allergic or non-allergic asthma (data not shown). Maternal smoking around pregnancy and birth was associated with increased early-onset asthma in offspring, most pronounced for the non-allergic phenotype (table 1). Paternal or maternal smoking only after the child’s birth was not associated with offspring asthma.

(Table 1 here)

Dose-response effect of paternal pre-conception smoking and non-allergic early-onset asthma in offspring
Both a father’s early smoking debut and a father’s longer smoking duration before conception increased non-allergic early-onset asthma in offspring, even with mutual adjustment and adjusting for number of cigarettes and years since quitting smoking (table 2). Early smoking debut was associated with more non-allergic early-onset offspring asthma even if the smoking stopped at least 5 years before the child’s birth (OR 2.68, 95% CI 1.17-6.13). A father’s smoking debut before age 11 (102 fathers) showed the greatest increased risk (OR=3.95, 95% CI=1.07-14.60), followed by smoking debut ages 11-14 (1.75, [1.07-1.86]), and smoking debut after age 15 (1.37, [1.00-1.86]). Longer duration of smoking was also associated with an increased risk, up to 1.8 fold for those smoking for more than 10 years (OR 1.76, 95% CI 0.96-3.25). Time of quitting before conception was not independently associated with non-allergic early-onset offspring asthma.

(Table 2 here)

**Relationship between paternal exposure to smoke in utero (grandmaternal smoking) and offspring non-allergic early-onset asthma**

Grandmaternal smoking status was associated with risk of non-allergic early-onset asthma in offspring (OR 1.3, 95% CI 1.0-1.6) and also modified the association between the father’s own smoking status and asthma in his offspring. If the paternal grandmother did not smoke, father’s own smoking before age 15 was associated with more non-allergic early-onset asthma in his children (table 3), but this association was not present if the paternal grandmother smoked (P\text{interaction}=0.02). In contrast, long smoking duration was associated with increased offspring asthma irrespective of whether or not the paternal grandmother smoked.

(Table 3 here)
Relationship between paternal occupational exposure to welding prior to conception and non-allergic early-onset asthma in offspring

Paternal welding starting prior to conception, but not welding starting after conception, was associated with increased non-allergic early-onset asthma in offspring (table 4). Welding increased offspring asthma risk even if the welding stopped prior to conception (aOR 1.56, 95% CI 0.99-2.46). Welding duration of at least ten years was associated with a greater increase in asthma (aOR 2.10, 95% CI 1.36-3.22) than welding for less than ten years (aOR 1.56, 95% CI 0.98-2.48).

Smoking and welding independently increased offspring asthma risk, and mutual adjustment did not alter the estimates of either. Offspring had more asthma if fathers were exposed to both smoking and welding (OR 3.6, 95% CI 1.7-7.6 for both smoking and welding for at least 10 years) (supplementary table 3). Welding duration for at least ten years was associated with more non-allergic early-onset asthma in offspring irrespective of grandmaternal smoking (no grandmaternal smoking: OR 1.9[1.01, 3.43]; grandmaternal smoking OR 2.8[1.34, 5.67], P_{interaction}=0.38).

(Table 4 here)

Heterogeneity between study centres

There was no evidence of heterogeneity between study centres for the effects of either paternal pre-conception smoking or welding prior to conception (Figure 1a and 1b).
DISCUSSION

Smoking and occupational welding in young men were associated with asthma risk in their children, even if these exposures occurred many years prior to conception. We identified several potential susceptibility windows for paternal environmental exposures, with the highest risk related to father’s smoking before completing puberty. Figure 2 shows our findings in the context of existing knowledge from laboratory and animal studies regarding vulnerability windows in sperm development. For smoking and welding starting after puberty, exposure duration appeared to be the most important determinant. These findings were consistent across geographical regions with different smoking habits and occupational exposures, and with different offspring asthma prevalence. These novel results suggest that environmental exposures in young men can have important impact on their future offspring’s respiratory health, and interventions aimed at adolescent men might have large public health consequences.

To our knowledge this is the first study investigating father’s environment prior to starting a family and the resulting asthma risk in his children. Our findings confirm an effect of father’s in utero exposure (grandmother’s smoking); Consistent with Miller and colleagues, we find that paternal exposure to his own mother’s smoking increased his children’s asthma risk. However, we also found effects of a father’s own preconception smoking.

Concerning mother’s smoking, we found more offspring asthma if the mother smoked around pregnancy, consistent with previous studies. However, no effect of maternal smoking prior to conception was identified. This has not previously been investigated, to our knowledge. Male and female germ cells develop differently. Further, if there is a prepuberty susceptibility window in females, this would be at a younger age than in boys, and at an age when the girls
have not yet started smoking. This could explain why we find an effect of preconception smoking in men but not in women.

Several lines of evidence suggest that the observed effects could be mediated through influences on spermatozoa development. The father’s but not the mother’s preconception exposure was associated with offspring risk, suggesting effects through male germ cells. Smoking is known to cause genetic and epigenetic damage to spermatozoa, which are transmissible to offspring and have the potential to induce developmental abnormalities.\textsuperscript{4,5,7,9} In utero smoking exposure of fathers could influence primordial germ cell development.\textsuperscript{3}

A prepubertal vulnerability window could be related to de-novo DNA methylation occurring during primordial germ cell differentiation to spermatogonia.\textsuperscript{30} Such a window is indicated by the observation of increased body fat in sons of fathers who smoked before age 11.\textsuperscript{10} There was higher offspring risk if the smoking started before completed puberty, but not in the case where father’s own mother smoked, suggesting that in utero exposure of primordial germ cells could induce adaptive responses preventing further damage to this cell stage during differentiation to spermatogonia in prepuberty, possibly by inducing specific maintenance mechanisms. Alternatively, there could be a threshold for damage of a certain exposure to this cell stage that is already reached by in utero exposure. After puberty, DNA methylation patterns are kept up through cycles of spermatogenesis. This could constitute another vulnerability window, requiring long exposure duration; our findings agree with findings of higher inheritable mutation frequency in murine spermatogonial stems cells with a longer duration of smoking exposure.\textsuperscript{7,31} We found little benefit from quitting smoking prior to conception, in agreement with findings of impaired DNA repair mechanisms in smoking exposed spermatozoa.\textsuperscript{32}
Smoking causes hormonal disruption, effecting hormonal and metabolic profiles. We found that men with early smoking debuts were shorter and heavier than never-smokers and men with later smoking debut. However, adjustment for paternal height, weight, or BMI did not attenuate the association with offspring asthma (data not shown), suggesting that early smoking effects on offspring asthma were not mediated through the impact on the father’s own growth and metabolic development.

The findings relating to occupational welding support the concept that young men’s environmental exposures impact their offspring’s health. Welding represents a complex, mixed exposure that is associated with cancer and respiratory diseases. In addition, groin heat that can affect spermatozoa. Animal studies have shown effects on sperm, which could affect subsequent generations.15-17

Father’s preconception exposures were related to a non-allergic asthma phenotype in offspring, suggesting that the effect is on lung function development rather than allergy (early frequent infections might be implicated). One may question whether growth and other chronic diseases in offspring might also be affected by father’s environmental exposures before parenthood.

The strengths of the present study include repeated detailed smoking assessment in a large cohort, allowing for analyses of effect modification and restricted subgroups (i.e. smoked only before conception). A limitation is the lack of information on smoking for the non-RHINE participating parent. As smokers’ spouses more often smoke themselves, this would attenuate observed differences between mother’s and father’s smoking effects; thus, true differences by parent gender may be larger than observed. Asthma status and birth year were missing for 1961 subjects with data on father’s smoking; sensitivity analyses suggested that this did not influence the results (online supplement). Lacking information on offspring’s own smoking is unlikely to have affected results on early-onset asthma.
Misclassification of offspring asthma is not likely to be differential with regard to parental smoking debut and duration. As parents might not be aware of their children’s asthma status after childhood, late onset asthma in particular could be underreported. Reporting bias is an unlikely explanation for the results as similar associations were seen when using exposure data collected ten years prior to collecting information about offspring (online supplement). The lack of detail with regard to asthma phenotype in the offspring is a limitation of the study. Confounding by socioeconomic status did not seem to explain our findings, as these changed little with adjustment for parental education, grand-parental education, and type of dwelling, and persisted in persons with tertiary educated parents (online supplement). An association between paternal smoking and offspring asthma was stronger in those who quit smoking prior to conception (higher educational level, less potential for recall bias) than in those who continued smoking after child birth (possibly more recall bias). We did not have information about the use of personal preventive equipment in relation to welding, but we controlled for paternal age at survey, which is likely to account for potential changes in exposures over time. The finding that smoking and welding starting after the child’s birth had no association with offspring asthma also supports a potentially causal effect. In general, while negative findings could be related to error, it is unlikely that systematic error has caused the observed associations. The potential role for unmeasured confounding in our positive findings must still be kept in mind.

In conclusion, our results suggest that father’s smoking and welding exposure prior to conception increased the risk for non-allergic early-onset asthma in his offspring, and that early smoking debut and long exposure duration substantially increased the risk, even if the father quit exposure years before conception. These results come from a large, population-based, multicentre study from Northern Europe, and are consistent between areas with different smoking and work habits and asthma prevalence. To our knowledge, this is the first study on
asthma risk in humans that investigates in detail the effects of paternal exposures prior to conception. Future research should attempt to replicate these findings in other populations. Mechanistic studies are now important to understand the detrimental effect of paternal pre-conception smoking and welding, as well as potential effect modification by *in utero* exposure. Such investigations might provide targets for intervention in terms of inducing protective mechanisms. Furthermore, we believe that it is urgent to investigate other potentially harmful exposures in young men, where occupational exposures may be particularly important in high-income as well as in low-income societies. Our findings should not lessen efforts to improve maternal health, which is crucial for offspring health, but they provide an unexpectedly strong argument for also focusing on the environment of young men.
Supplementary Data

Supplementary data are available at IJE online.

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Conflict of interest: The authors have declared that no competing interests exist.

Authors’ contributions

CS, AJ, BB, BF, TG, MH, CJ, RJ, EL, FM, AM, LM, DN, EO, EWS, TS, TDS, KT, VS and FGR carried out the studies included in the present paper, and participated in study design, coordination and data collection. JK and CS performed the statistical analyses, and drafted the manuscript together with SMS and FGR. SMS, AJ, RB, LB, AEC, SD, JD, TG, JH, MH, CJ, DJ, SKE, TS, ØS, and FGR participated with study design, development of ideas, analytical design and interpretation of the findings. CT contributed to analyses. All authors read and approved the final manuscript. CS and JK contributed equally to this manuscript.
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Table 1: Offspring asthma as associated with parental smoking patterns among 24168 offspring aged 2-51 years from 7 Northern European study centres.

<table>
<thead>
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<th>N</th>
<th>% asthma</th>
<th>OR* (95%CI)</th>
<th>p-value</th>
<th>N</th>
<th>% asthma</th>
<th>OR* (95%CI)</th>
<th>p-value</th>
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<td>father</td>
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<tr>
<td>EARLY ONSET ASTHMA</td>
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<tr>
<td>Parent never smoked</td>
<td>4715</td>
<td>7.5</td>
<td>1 (ref)</td>
<td>5488</td>
<td>8.3</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>Smoked only prior to conception</td>
<td>1148</td>
<td>9.5</td>
<td>1.37 (1.01-1.86)</td>
<td>0.044</td>
<td>1423</td>
<td>11.0</td>
<td>1.14 (0.88-1.47)</td>
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<td>Smoked including period around birth</td>
<td>3777</td>
<td>7.2</td>
<td>1.17 (0.93-1.48)</td>
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<td>4542</td>
<td>10.2</td>
<td>1.48 (1.22-1.78)</td>
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<td>Started after child’s birth</td>
<td>142</td>
<td>5.8</td>
<td>1.01 (0.42-2.43)</td>
<td>0.99</td>
<td>259</td>
<td>4.9</td>
<td>0.67 (0.33-1.38)</td>
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<td>Early onset allergic asthma†</td>
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<tr>
<td>Parent never smoked</td>
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<td>1.0</td>
<td>4221</td>
<td>3.8</td>
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<td>909</td>
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<td>0.60 (0.31-1.20)</td>
<td>0.15</td>
<td>1113</td>
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<td>95% CI</td>
<td>p-value</td>
<td>N</td>
<td>OR</td>
<td>95% CI</td>
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<td><strong>Early onset non-allergic asthma†</strong></td>
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<td>Parent never smoked</td>
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<td>9.3</td>
<td>1.68 (1.18-2.41)</td>
<td>0.004‡</td>
<td>1164</td>
<td>9.2</td>
<td>1.11 (0.81-1.52)</td>
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<td>Smoked including period around birth</td>
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<td>1.27 (0.96-1.69)</td>
<td>0.097</td>
<td>3610</td>
<td>9.0</td>
<td>1.65 (1.31-2.07)</td>
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<tr>
<td>Started after child’s birth</td>
<td>116</td>
<td>4.7</td>
<td>1.03 (0.35-3.05)</td>
<td>0.96</td>
<td>208</td>
<td>2.2</td>
<td>0.33 (0.10-1.03)</td>
</tr>
<tr>
<td><strong>LATER ONSET ASTHMA‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent never smoked</td>
<td>3627</td>
<td>2.8</td>
<td>1.0</td>
<td>1.0</td>
<td>4429</td>
<td>3.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Smoked only prior to conception</td>
<td>801</td>
<td>3.1</td>
<td>1.23 (0.73-2.04)</td>
<td>0.44</td>
<td>1046</td>
<td>2.9</td>
<td>0.79 (0.49-1.27)</td>
</tr>
<tr>
<td>Smoked including period around birth</td>
<td>3243</td>
<td>2.5</td>
<td>0.97 (0.69-1.38)</td>
<td>0.87</td>
<td>3903</td>
<td>4.3</td>
<td>1.13 (0.86-1.50)</td>
</tr>
<tr>
<td>Started after child’s birth</td>
<td>130</td>
<td>2.1</td>
<td>0.69 (0.19-2.53)</td>
<td>0.57</td>
<td>246</td>
<td>2.6</td>
<td>0.57 (0.22-1.44)</td>
</tr>
</tbody>
</table>

* OR adjusted for offspring age, parent characteristics (age, sex, early onset asthma, education) study centre, cluster by family.

† Baseline group for comparison was those with no asthma and no hay fever. Excludes those who developed asthma after age 10.

‡ Excludes those with early onset asthma and those under age 10 years
Table 2: Patterns of paternal smoking prior to conception in relation to early onset non-allergic asthma in their children

<table>
<thead>
<tr>
<th></th>
<th>OR* (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of smoking debut</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15 years</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&lt;15 years</td>
<td>3.24 (1.67, 6.27)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Duration (per 2 year increase)</strong>&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1.14 (1.03-1.26)</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Amount of smoking</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 cig/day</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>10-20 cig/day</td>
<td>1.42 (0.57-3.55)</td>
<td>0.45</td>
</tr>
<tr>
<td>&gt;20 cig/day</td>
<td>0.97 (0.36-2.64)</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Years before birth without smoking (per 2 years)</strong>&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>0.90 (0.78-1.04)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

* OR from analyses with mutual adjustment for the four smoking characteristics, and adjusted for offspring age, parent characteristics (age, early onset asthma, education) study centre, cluster by family.

† OR is per 2 year increase in smoking duration, with the baseline category set as those who smoked less than 1 year and a single upper category for those who smoked ≥ 21 years.

‡ OR is per 2 year increase in time before birth at which smoking stopped, with the baseline category set as those who stopped within 3 years of the child’s birth and a single upper category for those who stopped >15 years before the child’s birth.
Table 3: Father’s age of smoking debut and smoking duration prior to conception in relation to early onset non-allergic asthma in their children, stratified by paternal grandmothers’ smoking

<table>
<thead>
<tr>
<th>Paternal grandmother did not smoke</th>
<th>Paternal grandmother smoked</th>
</tr>
</thead>
<tbody>
<tr>
<td>N % asthma OR (95%CI)*</td>
<td>N % asthma OR (95%CI)*</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Father never smoked</td>
<td>2902 5.5 1.0</td>
</tr>
<tr>
<td>Father smoked before age 15</td>
<td>466 9.0 3.14 (1.68, 5.84)</td>
</tr>
<tr>
<td>Father smoked after age 15 and smoked &lt;10 years pre-conception</td>
<td>902 4.8 1.15 (0.65, 2.03)</td>
</tr>
<tr>
<td>Father smoked after age 15 and smoked ≥10 years pre-conception</td>
<td>1220 7.5 1.75 (1.09, 2.80)</td>
</tr>
</tbody>
</table>

- OR adjusted for offspring age, paternal characteristics (age, education, smoking status), grandparent education (grand-maternal and grand-paternal), study centre, cluster by family.

† Interaction P values calculated using the likelihood ratio test.
Table 4: Father’s exposure to occupational welding in relation to early onset non-allergic asthma in their children

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>% asthma</th>
<th>OR* (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early onset asthma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father never welding</td>
<td>6773</td>
<td>7.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Welding started prior to conception</td>
<td>1549</td>
<td>10.4</td>
<td>1.64 (1.25, 2.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Welding started after conception</td>
<td>305</td>
<td>7.5</td>
<td>1.14 (0.63, 2.05)</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Early onset allergic asthma†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father never welding</td>
<td>5521</td>
<td>2.6</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Welding started prior to conception</td>
<td>1232</td>
<td>3.1</td>
<td>1.31 (0.75, 2.28)</td>
<td>0.35</td>
</tr>
<tr>
<td>Welding started after conception</td>
<td>243</td>
<td>2.5</td>
<td>1.06 (0.34, 3.36)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Early onset non-allergic asthma†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father never welding</td>
<td>5706</td>
<td>5.8</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Welding started prior to conception</td>
<td>1317</td>
<td>9.3</td>
<td>1.80 (1.29, 2.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Welding started after conception</td>
<td>254</td>
<td>6.7</td>
<td>1.15 (0.55, 2.38)</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Later onset asthma‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father never welding</td>
<td>5473</td>
<td>2.7</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Welding started prior to conception</td>
<td>1192</td>
<td>3.6</td>
<td>1.42 (0.93, 2.19)</td>
<td>0.11</td>
</tr>
<tr>
<td>Welding started after conception</td>
<td>282</td>
<td>3.2</td>
<td>1.03 (0.45, 2.38)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

- OR adjusted for offspring age, paternal characteristics (age, education, smoking status), study centre, cluster by family.

† Baseline group for comparison was those with no asthma and no hay fever. Excludes those who developed asthma after age 10.

‡ Excludes those with early onset asthma and those under 10 years
References


