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

**ONLINE SUPPLEMENTARY MATERIAL**

**Sensitivity analyses and additional analyses**

*Sensitivity analysis to consider effect of missing data on the association between paternal pre-conception smoking and early onset non-allergic asthma*

Information on offspring asthma status and birth year were missing for 1,961 offspring with fathers participating in the study. We considered that parents might have been less likely to provide information on their child’s asthma status if the child did not have asthma. We therefore conducted a sensitivity analysis where all children with missing asthma status were assumed to be non-asthmatic. Where birth year was also missing, this was set as 1998 (mean birth year for participating offspring).This had little effect on the magnitude of the association between paternal pre-conception smoking and early onset non-allergic asthma (aOR for sensitivity analysis = 1·72, 95% CI 1·21-2·44, p=0·002).

*Sensitivity analysis to consider the effect of potential recall bias based on offspring asthma status on the association between paternal pre-conception smoking and early onset non-allergic asthma*

Information on parental smoking status was collected at two time points, 1999 (prior to collecting data about the child) and 2010 (at the same time as questions about child’s asthma status).To minimise the possibility of differential recall based on child’s reported asthma status, we examined the effect of paternal pre-conception smoking using only data collected in 1999 (prior to asking questions about the child). Parents who reported stopping smoking between 1999 and 2010 (n=2,742) or starting smoking after 1999 (n=27) were excluded from this sensitivity analysis. There was still an effect of paternal pre-conception smoking on early onset non-allergic asthma using only prospectively collected data (aOR for sensitivity analysis = 1·62, 95% CI 1·04, 2·52, p=0·032).

*Education/socioeconomic effect*

We controlled for education of the parents in the analysis and this made little difference to the associations. Additional adjustment for grand-paternal and grand-maternal education and type of dwelling also made little difference to the association between paternal smoking before 15 and offspring asthma: adjusted only for paternal education OR = 1·84, additional adjustment for grandparental education and dwelling type OR = 1·88. Fathers who started smoking early were more likely to have low education compared to those who never smoked, and slightly more likely to have low education compared to those who smoked later, but educational level of the father was not associated with early onset asthma in the child. Also, those who quit smoking prior to conception were more educated than those who continued smoking and were more similar to those who never smoked in terms of proportion with higher education. This makes it unlikely that the effect is due to confounding by education status. In support of this, we also still see a strong association between paternal smoking prior to conception and asthma in each educational class, including those with tertiary education (5·7% vs 9·8%, p=0·002). For welding, there were fewer welders who had tertiary education, but those who started welding after conception were actually more likely to have low education compared to those who started welding before conception (but did not have more children with asthma). There was also still a strong association between paternal welding prior to conception and asthma among those with a tertiary education (5·7% vs 11·5%, p<0·001).

**Supplementary Figure 1: Flow chart of study methods**

\*European Community Respiratory Health Survey1

†Respiratory Health in Northern Europe (RHINE)2

‡ RHINE follow up3

**Supplementary Table 1: Characteristics of study population and their parents by centre.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | All | Århus | Reykjavik | Bergen | Gothenburg | Umeå | Uppsala | Tartu |
| STUDY POPULATION (OFFSPRING) |  |  |  |  |  |  |  |  |
| *Number* | *24168* | *3865* | *4712* | *4517* | *2524* | *3283* | *3048* | *2219* |
| Asthma early onset < 10 years (%) | 8·5 | 9·1 | 11·5 | 7·4 | 6·7 | 8·9 | 8·4 | 4·3 |
| Early onset asthma with hay fever (%) | 2·6 | 2·4 | 3·1 | 2·4 | 2·7 | 2·8 | 3·2 | 1·2 |
| Early onset asthma without hay fever (%) | 5·8 | 6·7 | 8·4 | 5·1 | 4·0 | 6·0 | 5·3 | 3·1 |
| Asthma later onset >10 years (%)\* | 4·2 | 5·4 | 4·9 | 4·5 | 3·4 | 5·0 | 3·0 | 1·6 |
| Age (years, mean, range) | 22 (2-51) | 19 (2-51) | 24 (2-49) | 21 (2-45) | 23 (2-46) | 23 (2-48) | 22 (2-47) | 21 (2-44) |
| Birth year (mean, range) | 1988  1958-2010 | 1991  1959-2009 | 1986  1960-2009 | 1989  1965-2009 | 1987  1964-2008 | 1987  1962-2009 | 1988  1958-2009 | 1991  1968-2010 |
| PARENT |  |  |  |  |  |  |  |  |
| Age (years, mean, range) | 52 (38-66) | 50 (38-64) | 53 (40-66) | 51 (39-63) | 53 (40-65) | 53 (40-65) | 53 (40-65) | 49 (38-62) |
| Birth year (mean, range) | 1959  (1945-1973) | 1960  (1947-1972) | 1957  (1945-1970) | 1959  (1947-1971) | 1958  (1946-1970) | 1957  (1945-1970) | 1958  (1946-1970) | 1963  (1949-1973) |
| Number of children (mean, range) | 1·8 (1-8) | 1·7 (1-7) | 2·1 (1-8) | 1·8 (1-8) | 1·7 (1-6) | 1·9 (1-7) | 1·8 (1-7) | 1·8 (1-7) |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| FATHER  *Number* | *10977* | *1777* | *2170* | *2187* | *1091* | *1444* | *1391* | *917* |
| Asthma onset ≤10 years (%) | 3·7 | 2·9 | 2·7 | 4·5 | 4·0 | 4·5 | 4·6 | 1·4 |
| Asthma onset >10 years (%) | 6·8 | 4·7 | 8·5 | 7·5 | 5·5 | 6·7 | 7·2 | 5·0 |
| Never smoked (%) | 47·7 | 47·6 | 40·1 | 39·4 | 48·9 | 62·9 | 59·2 | 42·5 |
| Smoked only prior to conception (%)*†* | 13·0 | 12·2 | 16·5 | 12·3 | 12·3 | 13·2 | 12·5 | 9·0 |
| *Duration of smoking (years, mean, range)* | 9·2 (0-37) | 10·2 (0-31) | 10·2 (0-37) | 8·8 (0-32) | 10·4 (0-25) | 8·2 (0-30) | 9·4 (0-31) | 5·7 (0-29) |
| Any other smoking pattern (%) | 39·3 | 40·2 | 43·5 | 48·3 | 38·9 | 23·9 | 28·3 | 48·5 |
| *Mean duration of smoking before conception (years, mean, range)* | 12·1(0-39) | 14·3 (0-34) | 10·8 (0-39) | 12·4 (0-37) | 12·5 (0-32) | 12·2 (0-32) | 13·1 (0-36) | 9·0 (0-35) |
| Welding started prior to conception | 18·0 | 16·6 | 15·2 | 14·2 | 27·4 | 25·9 | 11·8 | 20·3 |
| *Duration of welding before conception (years, mean, range)* | 7·8 (0-32) | 6·9 (0-32) | 9·0 (1-27) | 7·5 (0-24) | 7·6 (0-20) | 8·3 (0-30) | 7·9 (0-23) | 6·5 (0-24) |
| Welding started after conception | 3·5 | 2·0 | 5·0 | 2·0 | 3·9 | 4·5 | 1·4 | 9·0 |
| MOTHER  *Number* | *13191* | *2088* | *2542* | *2330* | *1433* | *1839* | *1657* | *1302* |
| Asthma onset ≤10 years (%) | 2·7 | 2·1 | 2·1 | 2·3 | 2·2 | 2·9 | 4·6 | 2·7 |
| Asthma onset >10 years (%) | 10·2 | 8·1 | 13·3 | 10·4 | 7·8 | 11·3 | 9·3 | 8·0 |
| Never smoked (%) | 48·4 | 43·6 | 40·4 | 39·4 | 48·9 | 52·8 | 56·6 | 70·8 |
| Smoked only prior to conception (%)*†* | 12·5 | 15·4 | 16·8 | 12·2 | 11·2 | 10·9 | 12·1 | 4·5 |
| *Duration of smoking (years, mean, range)* | 7·7 (0-30) | 7·6 (0-23) | 8·0 (0-30) | 7·8 (0-27) | 8·5 (0-23) | 7·4 (0-24) | 8·3 (0-23) | 4·3 (0-15) |
| Any other smoking pattern (%) | 39·1 | 41·0 | 42·9 | 48·4 | 39·9 | 36·4 | 31·3 | 24·6 |
| *Duration of smoking before conception (years, mean, range)* | 9·9 (0-36) | 11·5 (0-30) | 9·0 (0-28) | 9·6 (0-36) | 10·2 (0-31) | 10·6 (0-29) | 10·7 (0-26) | 5·7 (0-24) |
| Welding started prior to conception (%) | *1·0* | *0·8* | *0·7* | *1·3* | *1·4* | *0·8* | *0·8* | *1·2* |
| *Duration of welding before conception (years, mean, range)* | 4·1 (0-17) | 2·7 (0-8) | 5·6 (1-8) | 3·9 (0-12) | 2·8 (1-7) | 1·9 (0-13) | 8·1 (0-17) | 4·8 (1-13) |
| Welding started after conception (%) | *0·7* | *0·6* | *0·8* | *0·5* | *0·9* | *0·9* | *0·1* | *1·2* |

\* Among those aged over 10 years (n=21517)

**†** Stopped smoking at least 3 months prior to conception

**Supplementary Table 2a: Characteristics of study population by maternal and paternal smoking**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Parent never smoked  (n=11,573) | Parent smoked only prior to conception  (n=2,706) | Parent any other smoking pattern  (n=9,796) | Parent started smoking before age 15  (n=2,482) | Parent started smoking after age 15 and smoked <10 years before conception  (n=4,020) | Parent started smoking after age 15 and smoked ≥10 years before conception  (n=4,618) |
| **FATHER** |  |  |  |  |  |  |
| Father age  (years, mean, range) | 50·9 (38·4-65) | 52·4 (38·7-65·1) | 53·7 (38·4-66) | 53·0 (38·6-65·2) | 53·6 (38·4-65·1) | 53·2 (38·4-65·0) |
| Father birth year  (mean, range) | 1960 (1946-1973) | 1958 (1945-1973) | 1957 (1945-1973) | 1957 (1946-1973) | 1957 (1945-1973) | 1957 (1945-1973) |
| Father asthma  onset ≤10 years (%) | 4·4 | 4·1 | 2·8 | 2·7 | 3·9 | 3·1 |
| Father asthma  onset >10 years (%) | 6·5 | 7·8 | 6·8 | 7·3 | 8·0 | 6·6 |
| Education: |  |  |  |  |  |  |
| *Primary (%)* | 6·6 | 8·7 | 16·8 | 22·2 | 14·4 | 13·6 |
| *Secondary (%)* | 39·0 | 42·0 | 47·8 | 50·3 | 44·4 | 46·0 |
| *Tertiary (%)* | 54·4 | 49·3 | 35·4 | 27·6 | 41·2 | 40·5 |
| Offspring age  (years, mean, range) | 19·0 (2-46) | 17·1 (2-41) | 24·0 (2-47) | 22·6 (2-44) | 26·2 (2-47) | 19·6 (2-39) |
| Offspring birth year  (mean, range) | 1991 (1965-2010) | 1993 (1969-2010) | 1986 (1960-2010) | 1988 (1967-2009) | 1984 (1964-2010) | 1990 (1971-2010) |
| Offspring asthma early onset <10 years (%) | 7·5 | 8·2 | 7·4 | 9·6 | 6·7 | 8·3 |
| Offspring asthma later onset >10 years (%) | 3·7 | 3·2 | 3·8 | 5·1 | 4·3 | 3·1 |
| Offspring early onset asthma with hay fever (%) | 2·5 | 1·3 | 2·0 | 2·6 | 2·0 | 1·6 |
| Offspring early onset asthma without hay fever (%) | 5·0 | 6·9 | 5·4 | 7·0 | 4·7 | 6·7 |
| **MOTHER** |  |  |  |  |  |  |
| Mother age  (years, mean, range) | 50·8 (38·3-65·4) | 50·4 (38·7-66) | 53·1 (38·5-65·1) | 50·8 (38·7-65·1) | 53·0 (38·6-65·1) | 52·2 (38·5-65·1) |
| Mother birth year  (mean, range) | 1960 (1945-1973) | 1960 (1945-1973) | 1957 (1945-1973) | 1960 (1945-1972) | 1957 (1945-1973) | 1958 (1946-1972) |
| Mother asthma  onset ≤10 years (%) | 2·7 | 2·6 | 2·7 | 3·3 | 2·4 | 2·2 |
| Mother asthma  onset >10 years (%) | 9·2 | 10·4 | 11·1 | 14·0 | 10·1 | 9·8 |
| Education: |  |  |  |  |  |  |
| *Primary (%)* | 8·3 | 7·2 | 18·3 | 19·1 | 15·9 | 11·8 |
| *Secondary (%)* | 35·7 | 34·9 | 45·5 | 43·4 | 44·7 | 41·6 |
| *Tertiary (%)* | 56·0 | 57·9 | 36·3 | 37·5 | 39·5 | 46·6 |
| Offspring age  (years, mean, range) | 21·6 (2-51) | 17·5 (2-43) | 25·8 (2-49) | 23·2 (2-49) | 27·1 (2-46) | 20·1 (2-39) |
| Offspring birth year  (mean, range) | 1989 (1958-2010) | 1993 (1968-2010) | 1984 (1961-2010) | 1987 (1961-2008) | 1983 (1964-2009) | 1990 (1971-2010) |
| Offspring asthma early onset <10 years (%) | 8·3 | 10·3 | 10·1 | 11·8 | 9·8 | 11·5 |
| Offspring asthma later onset >10 years (%) | 4·2 | 3·4 | 5·6 | 4·8 | 5·5 | 5·2 |
| Offspring early onset asthma with hay fever (%) | 2·9 | 3·2 | 3·0 | 3·9 | 3·1 | 2·8 |
| Offspring early onset asthma without hay fever (%) | 5·4 | 7·0 | 7·1 | 7·9 | 6·7 | 8·7 |

**Supplementary Table 2b: Characteristics of study population by paternal welding**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Father never welded  (n=6,773) | Welding started prior to conception  (n=1,549) | Welding started after conception  (n=305) | Welding only before conception  (n=632) | Welding <10 years before conception  (n=663) | Welding ≥10 years before conception  (n=842) |
| **Father** |  |  |  |  |  |  |
| Father age  (years, mean, range) | 52·4 (38·4-65·2) | 51·9 (38·7-65) | 54·0 (40·2-64·7) | 50·1 (38·7-64·8) | 50·5 (38·7-64·8) | 53·1 (39·4-65) |
| Father birth year  (mean, range) | 1958 (1945-1973) | 1959 (1946-1973) | 1957 (1946-1970) | 1960 (1946-1973) | 1960 (1946-1973) | 1957 (1946-1971) |
| Father asthma  onset ≤10 years (%) | 3·6 | 4·1 | 2·2 | 4·6 | 4·6 | 3·5 |
| Father asthma  onset >10 years (%) | 6·3 | 7·8 | 9·6 | 7·7 | 8·8 | 7·1 |
| Education: |  |  |  |  |  |  |
| *Primary (%)* | 9·3 | 14·4 | 21·7 | 8·7 | 9·2 | 18·1 |
| *Secondary (%)* | 36·9 | 60·3 | 54·3 | 53·0 | 51·7 | 67·7 |
| *Tertiary (%)* | 53·8 | 25·3 | 24·0 | 38·3 | 39·0 | 14·2 |
| Offspring age  (years, mean, range) | 20·7 (2-47) | 20·1 (2-45) | 28·2 (12-43) | 15·8 (2-43) | 17·8 (2-43) | 22·1 (2-45) |
| Offspring birth year  (mean, range) | 1990 (1964-2010) | 1990 (1966-2010) | 1982 (1967-1998) | 1995 (1967-2010) | 1993 (1967-2010) | 1988 (1966-2008) |
| Offspring asthma early onset <10 years (%) | 7·0 | 10·4 | 7·5 | 10·4 | 9·7 | 10·8 |
| Offspring asthma later onset >10 years (%) | 3·6 | 4·8 | 4·3 | 5·0 | 5·1 | 4·4 |
| Offspring early onset asthma with hay fever (%) | 2·1 | 2·5 | 2·0 | 2·1 | 2·1 | 2·6 |
| Offspring early onset asthma without hay fever (%) | 4·9 | 7·9 | 5·6 | 8·4 | 7·5 | 8·2 |

**Supplementary Table 3: Paternal smoking and welding exposures in relation to early onset non allergic asthma in their children**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **N** | **% asthma** | **OR 95%CI)\*** | **p-value** |
| Never smoked or welded | 2972 | 5·4 | 1·0 |  |
| Smoked before age 15, never welded | 469 | 8·5 | 2·20 (1·27, 3·80) | 0·005 |
| Welded at least 10 years, never smoked | 328 | 8·2 | 2·05 (1·09, 3·86) | 0·027 |
| Smoked before age 15 and welded at least 10 years | 76 | 11·8 | 3·56 (1·22, 10·34) | 0·019 |
| Smoked after age 15 for at least 10 years, never welded | 1195 | 7·1 | 1·45 (0·97, 2·16) | 0·071 |
| Smoked after age 15 for at least 10 years, welded for at least 10 years | 173 | 13·3 | 3·60 (1·72, 7·55) | 0·001 |

**References:**

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