Parental preconception BMI trajectories from childhood to adolescence and asthma in the future offspring

Abstract

Background: Recent evidence suggests that parental exposures before conception can increase the risk of asthma in offspring.

Objective: We investigated the association between parental preconception Body Mass Index (BMI) trajectories from childhood to adolescence and subsequent risk of asthma in their offspring.

Methods: Using group-based trajectory modeling from the Tasmanian Longitudinal Health Study (TAHS), we identified BMI trajectories for index participants (parents) when aged 4 to 15 years. Multinomial regression models adjusted for potential confounders were utilized to estimate the association between these early-life parental BMI trajectories and asthma phenotypes in their subsequent offspring.

Results: The main analysis included 1822 parents and 4208 offspring. Four BMI trajectories from age 4 to 15 years were identified as the best fitting model: “low” (8.8%); “normal” (44.1%); “above normal” (40.2%); and “high” (7.0%). Associations were observed between father’s “high” BMI trajectory and risk of asthma in offspring before the age of 10 years (RRR=1.70, 95%CI 0.98, 2.93) and also asthma ever (RRR=1.72, 95%CI 1.00, 2.97), especially allergic asthma ever (RRR=2.05, 95%CI 1.12, 3.72). These associations were not mediated by offspring birth weight. No associations were observed for maternal BMI trajectories and offspring asthma phenotypes.

Conclusion: This cohort study over six decades of life and across two generations suggests that the “high BMI” trajectory in fathers, well before conception, increased the risk of asthma in their offspring.

Keywords: Body Mass Index, preconception, intergenerational, transgenerational, epigenetics, asthma

Abbreviations used:

BMI: Body mass index, GBTM: Group-based trajectory modeling, TAHS: Tasmanian longitudinal health study, SNPs: Single nucleotide polymorphisms, ROS: Reactive Oxygen Species, BIC: Bayesian Information Criteria, IOTF: International Obesity Task Force

Capsule summary: Early onset and persistently high BMI in boys until puberty is associated with increased risk of asthma in their offspring.

Clinical Implications:

- "High BMI" trajectory among fathers was associated with increased risk of asthma in their offspring, and such association was not evident in mothers. Therefore, in males the risk in relation to the persistently high BMI trajectory may be targeted in early childhood rather than at puberty to reduce the risk of asthma in the next generation.

Introduction

There is increasing interest in understanding how parental health and lifestyle well before conception may impact on asthma in the offspring and subsequent generations. However, few epidemiological studies have been conducted of preconception exposures and asthma risk and asthma phenotypes in the next generation. One study found that a mother's exposure to smoking whilst she herself was *in utero* or being born to a father who started to smoke during puberty was associated with offspring asthma[1]. In contrast, being born to a mother who began to smoke during puberty was not associated with offspring asthma[2]. In a recent study, the role of father's prepubertal smoking onset was further supported by the impact on offspring lung function[3]. The biological plausibility of influence of pubertal exposures, specifically in the male line, might be explained by germ cell epigenetic mechanisms, where changes in germline epigenetic marks before conception can be transmitted across generations[4]. In females, all primary oocytes for her lifetime exist before birth or shortly after birth. However, the spermatogonia reserve germ cells in males do not undergo spermatogenesis until puberty,[5] and are thus open to prepubertal epigenetic modification. Therefore, adverse exposures to grandmothers during pregnancy of the future mother, or adverse exposures before puberty in future fathers may affect changes in gametes' genetic information that could be transmitted to the next generation[6].

Previous research has found that impaired spermatogenesis related to obesity is associated with stem cell epigenetic alterations, suggesting that epigenetic pathways of obesity and sperm quality could be transgenerational, thereby impacting offspring health[7]. Furthermore, a recent human study across two generations found that onset of overweight during puberty in fathers, but not in mothers, was significantly associated with an increased risk of non-allergic asthma, but not allergic asthma in their offspring[8]. However, in this study, the definition of pubertal overweight was based on recalled body silhouettes affected by a risk of confounding by misclassification of this exposure status. Thus, it is imperative to address this

potentially important topic in a cohort with lifetime longitudinal data on parental overweight from childhood to adolescence[8]. Furthermore, considerations of both onset as well as the progression of obesity (i.e., prospective trajectories of obesity) might provide a more accurate picture of how early-life weight changes affect future generations, compared to data on single time points over an individual's life course.

To overcome some of the limitations of commonly used methods to assess BMI over time group-based trajectory modeling (GBTM) has been used to track patterns of BMI through childhood and adolescence. This approach essentially incorporates latent class random effects analysis of growth trends and in doing so captures both individual's variation and modeling of the mean growth curves for each class[9].

We hypothesized that investigating such BMI trajectories through childhood and adolescence before future conception of offspring would provide more accurate insights than currently available into the influence of parental BMI on asthma in the next generation. Therefore, this study aimed to investigate the association between such preconception BMI trajectories in parents and risk of asthma of different phenotypes in their offspring and determine whether these associations differed by parental sex.

Methods

The study sample for this analysis included parents (original participants) and their offspring in the 53 year follow up of the Tasmanian Longitudinal Health Study (TAHS)[10-12]. Information regarding TAHS and its follow ups are described in Appendix I.

All the participants of the 53 year follow up (hereafter known as 'parents [mother and father]') were asked to provide information about their offspring (hereafter known as 'offspring') (Figure 1). Of the 3609 parents, 2556 provided information about their offspring including their asthma and allergy status. Parental reporting of offspring asthma was previously validated and the agreement was good [13]. The 2556 parents had 6,148 offspring (Figure 1), and the mean age of the latter was 23.4 (±6, range 0.5-38.9) years at the time of assessment. Hereafter, the parents of the original TAHS participants are known as "grandparents".

Parents' childhood and adolescent height and weight data were obtained from school medical records available in Tasmania. Information related to general health was reported in the school medical records as a routine practice. In this cohort, school medical records were available for only one parent of the offspring, that is, the original participants of the TAHS. The BMI data for the other parent were not available for analysis. We selected 15 years as the upper limit of parent age to calculate BMI, since the mean age of boys to complete puberty is 14.5 years and the environment might influence spermatogonia (the stem cell for spermatozoa development) throughout puberty after the process has commenced[2]. Previous studies investigating environmental exposures before puberty have similarly used the age 15 cut-off [2, 8].

Offspring asthma

Parents reported information was used to define presence and onset of offspring asthma using the questions, "Did this child have asthma before the age of ten years?" and "Did this child have asthma after the age of ten years?". "Ever asthma" was defined by a positive response to either of the two questions. The variable, "Asthma before and after 10 years" was created to have three categories: no asthma, asthma before 10 years and asthma after 10 years. "Ever asthma" was defined as either asthma before or after 10 years. "Ever allergic asthma" was defined as asthma plus eczema or allergic rhinitis ever [14]. Offspring who were <10 years old at the most recent TAHS follow up (53 years follow up) were excluded when classifying parent reported asthma in offspring before the age of 10 years. The reason for this exclusion was that these offspring <10 years still have a chance to develop asthma and could not be included in the definition: "offspring asthma before the age of 10 years".

Statistical analysis

BMI of parents for each age (from age 4 to 15 years) was calculated and standardized to the reference population for the child's age and sex with the use of UK reference growth charts using the STATA statistical package. Given not all had height and weight data for all time points (i.e., 4-15 years), BMI z-score values were combined into three groups ("early childhood": 4-6 years; "late childhood": 9-10 years; "adolescence": 14-15 years) in order to allow enough age points to be used in the trajectory modeling (Table S1). However, some of the age points (e.g., 7, 8, 9, 12 and 13 years) did not have sufficient BMI data to be included

in the trajectory modeling and were excluded from the analysis. Of the BMI data available, 3916 parents (of the 8583 TAHS original participants) had BMI data at all three age groups (Table S2). Availability of mother's and father's BMI data separately for ages 4-15 years is provided in Table S3.

Group-based trajectory modeling

The group-based trajectory modelling (GBTM) technique was used to identify distinct subgroups of individuals whose BMI z-score measurements showed a similar pattern over time. A finite set of unique polynomial functions, each corresponding to a discrete trajectory, was modeled by the GBTM [15]. Details of GBTM are given in Appendix II.

Parent BMI trajectories and offspring *asthma*

In the main analysis, we examined the association between BMI trajectory group variable (categorical variable) as the exposure and asthma variables as outcome variables using regression models. The "Normal BMI" trajectory group (Figure 1) was considered as the reference group in each model. The association between BMI trajectories and binary outcome variable "Ever asthma" was analyzed using binary logistic regression and asthma variables with three categories, "Ever allergic asthma (yes/no)" and "Asthma before and after 10 years" analyzed using multinomial logistic regression models.

For each model, a specific minimal sufficient set of potential confounders was selected on the basis of causal diagrams (directed acyclic graphs) using Dagitty software[16] (Figure S1). The potential confounders considered were mother ever-reported asthma at age 14 years, father ever-reported asthma at age 14 years, grandmother or grandfather ever asthma, if the grandmother or grandfather smoked during index parent's childhood, and grandfather`s occupation. Variables related to grandparents were collected in the TAHS 1968 baseline study. All analyses were stratified by the sex of the parents, given the hypothesis of sex-specific differences in the associations. Further, all the models were stratified by offspring sex to examine parent and offspring sex-specific effects. Finally, in the analysis all the regression models were clustered for family.

Sensitivity and mediation analyses

A set of sensitivity analyses were conducted to investigate the association between high BMI during puberty of parents and asthma in offspring in line with Johannessen *et al.* [17]. In addition, a mediation analysis was performed to investigate mediating effects of birth weight of the offspring on father's overweight and offspring asthma (Appendix III).

All unadjusted models, including logistic and multinomial logistic regression models, included only complete cases where all the exposure, outcomes and confounder variables were available. Therefore, the number of observations in both unadjusted and adjusted models was the same. All statistical analyses were performed using STATA version 15.1 (Stata Corporation, College Station, Texas, USA).

Results

Participant characteristics

Of the 2556 parents who provided information on their offspring, 1822 (836 fathers and 986 mothers) also had sequential, objective and independent information on their BMI, and their 4208 offspring were those included in the main analysis. In total, BMI trajectories were developed for 6921 TAHS parents (Figure 1), and there was no difference between the profile of BMI trajectories of parents included in the analysis (n=1822) and those not included in the analysis (n=5099) (Table S4). Table 1 shows the parent and respective grandparent characteristics according to father and mother. The prevalence of ever childhood asthma in parents when they had been 14 years old was higher in subsequent fathers (18.2%) compared to subsequent mothers (10.9%).

Grandfather occupation category was similar in both mothers and fathers. However, combined grandparent smoking rates were slightly higher in the mothers (68.0%) compared to the fathers (63.6%) (Table 1). In offspring, ever asthma in mothers was comparatively high (29.1%) compared to asthma in the fathers (22.9%) and ever-allergic asthma was also higher in these mothers (21.5%) compared to the fathers (14.3%) (Table 2).

BMI Trajectories

The best fitting BMI trajectory model, developed using BMI z-scores, had four trajectories (n=6921) (Figure 2). In this model the average posterior probability of each trajectory

exceeded 0.7, suggesting good model adequacy. After considering the trend in each trajectory group, they were labeled as 'Low BMI' (8.8%), 'Normal BMI' (44.1%), 'Above normal BMI' (40.2%), and 'High BMI' (7.0%) (Figure 2, Table S5). The prevalence of "High BMI" was slightly higher in mothers (6.39%) compared to fathers (4.67%) (Figure 2), but overall the distributions of all trajectories appeared to be quite similar (Figure S2). For each BMI trajectory, the raw mean BMI score, range, and standard deviation for each age group by sex are given in the Supplementary Table S6. We found similar BMI trajectories after restricting the analysis to participants with data for all time points (n=3919) (Figure S3). There was no difference in offspring asthma prevalence between parents with such complete BMI data and those with partially missing BMI data in whom we used GBTM with maximum likelihood estimation to allow for missing BMI time points (Table S7).

Parent BMI trajectories and offspring asthma

The associations between BMI trajectories of parents when aged 4 – 15 years and asthma in their subsequent offspring (ever, before and after age 10 years) are reported in Table 3. Compared with the "Normal BMI" trajectory, the "High BMI" trajectory in parents showed a trend of association with offspring ever-asthma, and asthma both before and after age 10 years. Both ever asthma risk in offspring and asthma before 10 years were associated with father's "High BMI" trajectory (RRR 1.72, 95%CI 1.00, 2.97 and RRR 1.70, 95%CI 0.98, 2.93, respectively). No associations with offspring asthma were found in mothers (Table 3).

Parental BMI trajectories and offspring allergic asthma

In adjusted and unadjusted models, the "High BMI" trajectory compared with the "Normal BMI" trajectory showed a trend of association only with ever allergic asthma. In the sex-stratified analysis, only the "High BMI" trajectory of fathers was associated with offspring ever allergic asthma (RRR 2.04, 95%CI 1.12, 3.72 (p=0.02)). No significant associations were found or any other BMI trajectory, non-allergic asthma or in mothers (Table 4).

Fathers' BMI trajectories and offspring asthma – stratified by offspring sex

In this stratified analysis the significant effects of fathers' "High BMI" trajectory on ever asthma and ever allergic asthma in offspring were mainly seen in the female offspring (Tables S8 & S13).

Sensitivity analyses

In line with a previously published analysis[8], a sensitivity analysis based on obesity, defined using the international cut off points for BMI, showed a pattern of the "obese" parent group being associated with increased odds of asthma in their offspring, although mainly in fathers. This association at the age of 15 years was mainly observed among obese fathers and allergic asthma in offspring RRR 2.36 (0.98, 5.69) (Tables S14 and S15). However, the associations were not as clear-cut when using the international cut off points at the ages of 5 and 10 years compared to childhood BMI trajectories in parents were used (Tables 16-19). Furthermore, the sensitivity analyses using BMI during puberty as a continuous variable and categorical variables (binary BMI; obese and non-obese, quartiles, and a categorical variable classified using standard deviations) provided similar results as BMI trajectories (Tables S20 and S25). However, none of the findings of these additional analyses were as consistent or strong as the trajectory analysis.

Mediation through offspring birth weight

There was no mediation by offspring birth weight observed for the association between fathers' overweight and offspring asthma or its allergic phenotype (Table S26).

Discussion

We identified that a "High BMI" trajectory from childhood to adolescence in fathers was associated with an increased risk of allergic asthma in their offspring, while this association was not seen in mothers. Our mediation analysis did not find offspring birth weight itself to mediate this father-offspring association.

To our knowledge, this is the first study to prospectively use parental BMI trajectories from their childhood to adolescence, which accounts for dynamic variations in BMI to investigate asthma risk in their offspring. However, our results are consistent with the recent European cohort study that showed that being overweight during prepuberty in males increased the risk of asthma in subsequent offspring. Furthermore, unlike our more objective longitudinal data, Johannessen et al. defined parental overweight using only retrospective information gathered on body shape using a single time point. On the other hand, Johannessen et al. used offspring information collected from the offspring themselves, supporting our study using parental reported information. The consistency of message in these two differently designed studies, using different definitions of exposures and outcomes, and different statistical approaches, greatly strengthens the evidence that paternal prepubertal obesity may have key importance for future offsprings' health[17].

Asthma is a complex condition with various phenotypes and is associated with both heritable and environmental risk factors. Up until now, the heritable mechanisms have been explained by genetic sequence variation such as single nucleotide polymorphisms (SNPs) using both candidate gene and genome-wide association approaches[18]. However, these variations alone are unable to explain either the total heritability of asthma or the increased prevalence of asthma over recent decades [19]. Developmental programming in mammals is thought to account for how early life exposures could increase disease risk in later life, either via altered developmental trajectories or epigenetic mechanisms. The observation that the effects of environmental exposure in mammals may be transmitted through more than one generation indicates that some epigenetic factors can be transferred through generations in a process known as transgenerational epigenetics[20, 21 22]. There is accumulating evidence from animal studies and a few limited epidemiological studies to suggest that transgenerational epigenetics are important in allergic disease outcomes [22].

Previous studies have demonstrated that environmental exposures can induce epigenetic changes (e.g., air pollutants, heavy metals, polycyclic aromatic hydrocarbons and persistent organic pollutants) [23] and also lifestyle factors, e.g., diet, obesity, physical activity levels, tobacco smoking, alcohol consumption and psychological stress[24]. In particular, epigenetic changes that occur during the differentiation of stem cells for gametogenesis have the potential to be transferred to the next generation. This is consistent with the outcome of our study where we observed an increased risk of allergic asthma in offspring only through the fathers, and not the mothers.

Previous research suggests that in males epigenetic signatures (such as methylation patterns) are established at the time of germ cell differentiation, highlighting a susceptible developmental window exposed to environmental and lifestyle factors[25]. However, for females, gametogenesis is initiated in utero and all primary oöcytes are produced and exist before birth[5], and so are not susceptible to such late post-partum influences. This provides one possible explanation why only fathers' high BMI during childhood and adolescence could be associated with offspring asthma. There are only a limited number of human studies investigating the potential effects of obesity on sperm stem cell epigenetics [26]. Obesity or high levels of fatty acids are associated with increased levels of reactive oxygen species (ROS) [27 28] and altered ROS balance may drive DNA methylation and changes in the chromatin structure of spermatogonia DNA, essential factors in epigenetic processes [29]. Although the exact mechanisms are not fully elucidated, these findings shed some light on our understanding of how a "High BMI" during adolescence could be imprinted in the sperm epigenome and thereby transfer adverse health effects to offspring [30]. A previous study has shown that BMI at one time point during puberty was a predictor of asthma in offspring, which was supported by our sensitivity analyses. However, BMI may change over time during childhood and adolescence, thus the role of high BMI on offspring's asthma may depend on the BMI timing as well as the longitudinal changes. Therefore, investigation of BMI trajectories could provide better insights to the impact of BMI on offspring asthma. Moreover, understanding of BMI patterns and their impact may better inform preventive interventions to avoid disadvantaged BMI trajectories. For example, the risk in relation to the persistently high BMI trajectory may be targeted in early childhood rather than later during puberty. Detailed supplementary

analyses findings for an association between BMI at one time point and offspring asthma highlight our trajectory approach's advantage.

Birthweight data for offspring were used in the mediation analysis, which enabled us to explore any effects of the offspring's own BMI on the association between parental BMI during their own adolescence and subsequent offspring asthma. No mediation by personal birth weight was found. Johannessen *et al.* used offspring BMI at the age of 8 years as a mediator for the association between fathers being overweight at puberty and their offspring asthma. They also found no such indirect effect [17]. We speculate that these findings both suggest an impact of paternal overweight on mechanisms related to inflammation, beyond mechanisms pertaining to growth and obesity. However, in contrast to the current study, Johannessen *et al.* [17] found that fathers being overweight during puberty was associated with non-allergic asthma rather than allergic asthma in their offspring. In our study, the prevalence of allergic asthma in offspring was 14.3% in the fathers and 21.5% in the mothers, compared with just 9.3% and 10.2%, respectively, in the European study [17]. The differences in associations with allergic vs. non allergic asthma between our study and that of Johannessen et al., may be related to a number of factors. The offspring were much younger in the current study (0.5 – 39 years) than in Johannessen et al., (18-50 years), and our definition of allergic asthma was broader. Moreover, the allergic phenotypes in the two studies may be different due to geographical (Europe vs. Australia) differences, in general allergies are reported to be more frequent in Australia than in Northern Europe. Also, the reporting was different in the two studies. Therefore, the results regarding allergic asthma phenotype vs. non-allergic asthma phenotype in these two different settings should not be given too much weight.

Prospective investigations of transgenerational effects in humans are difficult due to the long lifespan of humans. Therefore, almost all studies conducted in this emerging field of research to date have used recall data or proxy variables, especially for exposures that were decades in the past. Thus, for example, Johannessen *et al.* [17] used recognition of body silhouettes to characterize non-overweight and overweight subjects at earlier life stages in their study. Their non-allergic asthmatic parents may have overestimated their childhood body shape given that adult obesity is itself a potential cause of adult-onset non allergic asthma. Furthermore, obesity in both parents and children could be related to shared environmental factors.

Alternatively, lack of such non differential error in recalling childhood obesity among allergic asthmatics may have pushed the association towards null.

The "High BMI" trajectory was consistent throughout ages 5 to 15 years without overlapping with other trajectories. This pattern has been observed by other studies with any overlap with other trajectories occurring before 5 years[31, 32]. According to previous literature after 5 years no considerable overlap was observed in this "High BMI" trajectory group[33-36]. This group might include individuals influenced by both genetic and obesogenic environment that determine early development of obesity [37]. Therefore, our "High BMI" group is likely to consist of both genetically-predisposed and environmentally-induced overweight individuals.

Strengths and Limitations

The major strength of the TAHS is its longitudinal study design and prospectively collected and detailed data. In particular, for this analysis parent BMI data were obtained from height and weight data recorded in systematic sequential school medical records. The BMI during childhood and adolescence is dynamic, which may not be accurately captured by using just one single time point. To overcome this issue, we used BMI trajectories using all the data available. Our findings from the trajectory analyses were consistent with our sensitivity analyses using a single time point BMI as a categorical variable. However, single time point BMI as an exposure did not demonstrate as clear signals as the trajectory analysis although results were in the same direction. To explore the importance of specific ages, and we analyzed BMI as a categorical variable for obesity at the single time points of ages 5 and 10 and 15 years, however, the findings were not consistent or strong as the trajectory analysis (Tables S14 – S19). Furthermore, in the statistical models we included potential variables from three generations and models were adjusted not only for the parent's generation, but also for grandparents.

However, our study also had a few limitations. BMI data obtained from the school medical records were not complete for all the parents. However, we addressed this issue by combining some of the age groups together and forming three combined BMI groups that were used in the trajectory modeling. In the present analysis, BMI information was available to us only for one parent of the offspring, either mother or father who had been involved in

TAHS. However, as TAHS is a whole of population, cohort study and so was not focused on recruiting specifically overweight or obese individuals, the chance of recruiting a higher number of overweight or obese participants in one group (i.e., fathers or mothers) was unlikely. Since one parent's BMI was missing in each instance, this was a limitation in the TAHS study design as applied to this specific question. In the study by Johannessen *et al*[17], one of their models was adjusted for the other parent's overweight as reported by the offspring. However, they did not find that this made any difference to outcomes. In the mediation analysis, we have used parent-reported birthweight of offspring at the 53 year follow up. Recalling the birthweight of offspring by parents is associated with non-differential misclassification. In addition, a systematic review including 40 studies reported that there is a good agreement between parent recalling of birthweight of their offspring regardless of the recalling timescale[38]. When defining asthma onset (ever asthma before or after 10 years), participants aged less than 10 years were excluded. However, this group comprised only 0.01% of the sample and therefore the influence on the analysis was minimal. In this study, we did not adjust for multiple tests as we focused on a predefined hypothesis based on biological plausibility and interpreted overall patterns of associations. When stratified by fathers and mothers, our key findings on the high BMI group are consistent with what is hypothesized, with relatively narrow confidence intervals suggesting sufficient power. Nevertheless, it is important to acknowledge that in such stratum specific estimated effects should be interpreted with caution, and these findings require further replication. In our sensitivity analysis, we found that categorizing zBMI into different categories might not account for the potential variations in BMI and fluctuations between those categories during a short period of time. The effect of genetics cannot be completely ruled out since it was not accounted for in this analysis. In our study neither maternal BMI during pregnancy nor weight gain during pregnancy were available. Therefore, we could not stratify the analysis for or examine the mediating effect by these maternal factors. There may also be some unmeasured confounding factors that we could not include in the analyses such as infections, poor diets and lifestyle factors that were specially related to the High BMI trajectory, though these would be unlikely to be gender specific.

Conclusions

We found that fathers' “High BMI” trajectory during their earlier childhood and adolescence was associated with asthma before 10 years and ever asthma in their subsequent offspring, which was especially evident for ever allergic asthma. Obesity has been a rapidly growing global health concern of epidemic proportions for some decades, including in children and young adults. Obesity during childhood and adolescence is not only associated with a higher risk of diseases over the life course, but also transfers health risks to future generations though epigenetic mechanisms. Our study strengthens findings from previous research on the inheritance of risk factors for asthma across generations, with the key events occurring well before subsequent conception. Thus, our findings highlight the necessity for all of government public health policy and practice change to improve the health of children and adolescents, not only to benefit their own health in the future, but also the health of generations to come.

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Figure descriptions:

Figure 1: Follow ups of the Tasmanian Longitudinal Health Study

Figure 2: Parent BMI Trajectory Groups of Tasmanian Longitudinal Health Study. Dotted lines indicate 95% confidence intervals

589 **Table 1: Characteristics of parents and grandparents**

Characteristics		Fathers n = 836	Mothers n = 986	Fathers not included in the analysis n =2,739	Mothers not included in the analysis n = 2,448	P**	P***
Parents		%(Count)	%(Count)	%(Count)	%(Count)		
Asthma ever reported at the age of 14 years	Yes	18.2 (152)	10.9 (107)	16.5 (453)	10.7 (263)	0.27	0.92
Grandparents							
Grandmother/grand-father ever asthma*	Yes	19.3(161)	17.7 (175)	19.6 (536)	18.3 (449)	0.11	0.06
Grandmother/grand-father smoked*	Yes	63.6 (532)	68.0 (670)	64.0 (1,754)	65.9 (1,613)	<0.01	0.02
Grandfather occupational category	Managers	16.0 (134)	14.4 (142)	11.1 (303)	10.6 (260)	<0.01	0.01
	Professionals	9.4 (79)	8.9 (88)	6.5 (178)	7.0 (171)		
	Associate Professionals	6.7 (56)	7.5 (74)	5.4 (147)	6.0 (148)		
	Tradespersons	22.7 (190)	25.6 (252)	26.4 (722)	24.8 (606)		
	Advanced Clerical	3.5 (29)	3.4 (34)	2.5 (69)	2.4 (58)		
	Intermediate clerical	8.5 (71)	9.8 (97)	8.6 (236)	7.9 (193)		
	Intermediate production	20.3 (170)	18.0 (177)	19.3 (529)	18.4 (451)		
	Elementary clerical	2.0 (17)	2.1 (21)	2.4 (67)	2.2 (54)		
	Laborers & related	10.8 (90)	10.2 (101)	11.8 (324)	13.3 (326)		

590 * Self reported by Grandparents when parents (TAHS original participants) were 7 years old

591 **P value, between fathers included and not included in the analysis, *** P value between mothers included and not included in the analysis

592 **Table 2: Characteristics of the offspring**

593

		Father n = 1938	Mother n = 2270	P*
		%(Count)	%(Count)	
Ever asthma	Never asthma	76.8 (1,488)	70.6 (1,602)	<0.01
	Ever asthma	22.9 (445)	29.1 (662)	
Asthma status	Never asthma Asthma before age 10 years Asthma only after age 10 years	76.8 (1,488) 20.2 (392) 2.7 (53)	70.6 (1,602) 24.6(559) 4.5 (103)	<0.01
Ever allergic and non allergic asthma	Never asthma Ever non-allergic asthma Ever allergic asthma	76.8 (1,488) 8.5 (164) 14.3 (278)	70.6 (1,602) 7.5 (170) 21.5 (488)	<0.01
Sex	Male	50.6 (981)	51.2 (1,163)	0.84
Age, years (SD)		22.3 (5.3)	24.9 (5.3)	<0.01
Birth weight, kg (SD)		3.4 (0.6)	3.4 (0.6)	0.43

594 **P value, between fathers and mothers

595 **Table 3:** Association between parental Body Mass Index (BMI) trajectories (from 4 – 15 years) and offspring asthma (before or after 10 years).

	Low BMI		*Above normal*		*High BMI*	
	Unadjusted RRR (95% CI) p	Adjusted* RRR (95% CI) p	Unadjusted RRR (95% CI) p	Adjusted* RRR (95% CI) p	Unadjusted RRR (95% CI) p	Adjusted* RRR (95% CI) p
Ever asthma (Number of offspring n = 4,208 offspring [1,822 parents])						
Ever asthma	1.00 (0.73,1.38) 0.99	1.00 (0.73,1.36) 0.97	1.09 (0.92,1.30) 0.32	1.09 (0.92,1.30) 0.33	1.41 (1.00,1.99) 0.05	1.37 (0.97,1.94) 0.08
Sex stratified analysis for fathers n= 1,938 offspring (836 fathers)						
Ever asthma	0.98 (0.60,1.60) 0.93	1.02 (1.62,1.66) 0.94	1.09 (0.84,1.42) 0.53	1.05 (0.81,1.38) 0.70	1.67 (0.97,2.88) 0.06	1.72 (1.00,2.97) 0.05
Sex stratified analysis for mothers n = 2,270 offspring (986 mothers)						
Ever asthma	1.00 (0.66,1.51) 0.99	0.97 (0.64,1.46) 0.87	1.08 (0.86,1.36) 0.49	1.10 (0.87,1.39) 0.43	1.22 (0.78,1.91) 0.39	1.13 (0.71, 1.78) 0.61
Asthma before or after 10 years (Number of offspring n = 4,197 [1,818 parents])						
before 10 years	1.04 (0.74, 1.45) 0.83	1.04 (0.74, 1.45) 0.82	1.05 (0.87, 1.26) 0.63	1.04 (0.87, 1.26) 0.65	1.37 (0.97, 1.95) 0.08	1.36 (0.95, 1.93) 0.09
after 10 years	0.65 (0.27, 1.61) 0.36	0.63 (0.26, 1.56) 0.32	1.43 (0.98, 2.09) 0.07	1.44 (0.98, 2.11) 0.06	1.76 (0.84, 3.68) 0.13	1.59 (0.76, 3.32) 0.22
Asthma before or after 10 years - S*tratified analysis for fathers (fathers, n = 834) of 1933 offspring*						
before 10 years	1.00 (0.60, 1.66) 1.00	1.06 (0.63, 1.77) 0.84	1.04 (0.79, 1.38) 0.78	1.01 (0.76, 1.34) 0.95	1.63 (0.95, 2.83) 0.08	1.70 (0.98, 2.93) 0.06
after 10 years	0.56 (0.13, 2.47) 0.42	0.55 (0.12, 2.41) 0.43	1.36 (0.72, 2.57) 0.44	1.34 (0.70, 2.54) 0.38	2.06 (0.65, 6.48) 0.22	2.05 (0.64, 6.55) 0.22
Asthma before or after 10 years - S*tratified analysis for mothers (mothers, n =984) of n=2,264 offspring*						
before 10 years	1.04 (0.67, 1.63) 0.85	1.02 (0.66, 1.57) 0.95	1.04 (0.81, 1.33) 0.76	1.05 (0.82, 1.34) 0.70	1.19 (0.75, 1.88) 0.46	1.10 (0.69, 1.77) 0.69
after 10 years	0.68 (0.22, 2.07) 0.49	0.65 (0.21, 1.99) 0.45	1.44 (0.89, 2.33) 0.13	1.48 (0.91, 2.40) 0.11	1.52 (0.59, 3.92) 0.39	1.41 (0.55, 3.59) 0.47

596 RRR = Relative Risk Ratio, 95%CI = 95% Confidence Interval

597 In the analysis "Normal BMI" was considered as the reference group in the independent variable and "No asthma" in the dependent variable.

598 *Adjusted for parent's ever asthma, grandmother's or grandfather's ever asthma, whether grandmother or grandfather smoked during

599 parent's childhood and grandfather's occupation. Offspring <10 years of age at the most recent TAHS follow up (parent aged 53 years)
600 excluded from the analysi

Table 4: Association between parent BMI trajectories (from 4 – 15 years) and offspring ever allergic asthma or ever non-allergic asthma

Number of offspring n = 4,203 (1,820 parents)						
	Low BMI		*Above normal*		*High BMI*	
	Unadjusted RRR (95 % CI) p	Adjusted* RRR (95 % CI) p	Unadjusted RRR (95 % CI) p	Adjusted* RRR (95 % CI) p	Unadjusted RRR (95 % CI) p	Adjusted* RRR (95 % CI) p
Allergic or non allergic asthma						
Ever non-allergic asthma	1.07 (0.64,1.78) 0.79	1.12 (0.67,1.86) 0.67	1.14 (0.88,1.49) 0.31	1.14 (0.87,1.49) 0.33	1.26 (0.73,2.18) 0.41	1.26 (0.72,2.20) 0.42
Ever allergic asthma	0.98 (0.69,1.39) 0.89	0.94 (0.67,1.33) 0.73	1.06 (0.86,1.31) 0.57	1.07(0.86,1.31) 0.55	1.45 (0.98,2.15) 0.06	1.40 (0.94,2.09) 0.09
Allergic or non allergic asthma - S*tratified analysis for fathers (fathers, n = 834) of 1934 offspring*						
Ever non-allergic asthma	1.02 (0.51,2.05) 0.96	1.10 (0.55,2.18) 0.78	1.04 (0.72,1.52) 0.83	1.01 (0.69,1.49) 0.96	1.00 (0.37, 2.75) 0.99	1.07 (0.39,2.97) 0.89
Ever allergic asthma	0.95 (0.54,1.69) 0.86	0.98 (0.55,1.73) 0.92	1.09 (0.78,1.51) 0.62	1.05 (0.76,1.48) 0.75	2.01 (1.11,3.62) 0.02	2.04 (1.12,3.72) 0.02
Allergic or non allergic asthma - S*tratified analysis for mothers (mothers, n = 989) of* 2,282 *offspring*						
Ever non-allergic asthma	1.13 (0.54,2.34) 0.74	1.17 (0.57,2.42) 0.67	1.26 (0.87,1.82) 0.22	1.28 (0.88,1.87) 0.19	1.48 (0.77,2.85) 0.24	1.40 (0.71,2.75) 0.33
Ever allergic asthma	0.96 (0.61,1.49) 0.85	0.89 (0.58,1.38) 0.61	1.03 (0.79,1.34) 0.82	1.05 (0.80,1.37) 0.74	1.14 (0.67,1.93) 0.64	1.05 (0.62,1.78) 0.85

In the analysis “Normal BMI” was considered as the reference group in the independent variable and “No asthma” in the dependent variable. * Adjusted for parent’s ever asthma, grandmother’s or grandfather’s ever asthma, if grandmother or grandfather smoked during parent’s childhood and grandfather’s occupation. Offspring <10 years of age at the most recent TAHS follow up (parent aged 53 years) excluded from the analysis.