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The association of the 'additional height index' with atopic diseases, non-atopic asthma, ischaemic heart disease and mortality: a population-based study

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ABSTRACT

Objective: Intrauterine growth has been associated with atopic conditions. Growth and adult height have been associated with cardiovascular disease, cancers and mortality but are highly genetic traits. The objectives of the study were as follows: first, to define a height measure indicating an individual's height below or above that which could be expected based on parental height (genetic inheritance) and growth charts. It was named 'the additional height index' (AHI), defined as (attained—expected) height; second, to investigate possible associations of AHI with atopic versus non-atopic health outcomes and with ischaemic heart disease (IHD) and IHD mortality.

Design: General population-based study.

Setting: Research centre.

Participants: A random sample of 2656 men and women living in greater Copenhagen took part in the MONICA10 study (the Danish monitoring trends and determinants of cardiovascular disease). In total, 1900 participants with information of parental height were selected.

Outcome measures: Atopic sensitisation (serum IgE), questionnaire information of atopic dermatitis, rhinoconjunctivitis, asthma or wheezing, and registry-based diagnoses of IHD/IHD mortality from National Registries.

Results: Increasing levels of AHI were inversely associated with non-atopic asthma, non-atopic wheezing, IHD and IHD mortality (IHD-all). For one SD increase of AHI, the OR or HR with CI in adjusted analyses was non-atopic asthma OR=0.52 (0.36 to 0.74), non-atopic wheezing OR=0.67 (0.51 to 0.89), and IHD-all HR=0.89 (0.78 to 1.01). The level of AHI was higher among individuals with atopic dermatitis, allergic rhinoconjunctivitis and atopic sensitisation (all p values <0.001) compared with individuals without those conditions; however, the associations were not confirmed in adjusted analyses.

Conclusions: Individuals with childhood conditions that led them to attain tallness higher than expected from their parents' height may be at lower risk of non-atopic asthma/wheeze and IHD/IHD mortality but possibly at higher risk of atopic conditions. The measure of tallness below or above the expected height could be a sensitive alternative to normal height in epidemiological analyses.

Strengths and limitations of this study

- The strengths include he definition of a new height measure, the 'Additional Height Index'. It is designed to take genetic inheritance in height into account when using height measures in epidemiological studies.
- A population-based cohort of 1900 adults with blood samples to test for atopic sensitisation and follow-up of participants in national registries.
- The design of the additional height index is not validated and the study is based on a single cohort.

INTRODUCTION

The prevalence of allergic diseases has increased worldwide, apparently in parallel to increasing affluence,[1] first in westernised countries followed by low-income and middle-income countries.[2–4] Possible explanations have included improved hygiene and decreasing sibship size, for example, leading to fewer infections.[5–8] However, a secular change along with increasing affluence and hygienic standards is health-focused behaviour in these societies, for example, parental focus on nutrients and frequent meals for their children. This most likely contributes to the increased prenatal and postnatal growth of children as well as increased growth in adolescence that has been observed in different countries and ethnic groups following affluence.[9–12] Since the rise in allergic diseases has developed in parallel with these changes in growth and health-focused behaviour, it may be speculated that factors leading to increased

growth also can induce, for example, changes in the immune system towards an increased susceptibility to allergies.

Childhood health is supposedly reflected by balanced growth during gestation, through early infancy to adulthood, and children who do not follow the normal growth pattern seem to have a higher risk of different diseases. For instance, small babies who exhibit catch-up growth have an increased risk of developing cardiovascular diseases (CVDs), impaired lung function and asthma compared with small babies who stay small.[13 14] Catch-up growth may also be more predictive of childhood asthma than birth weight and length, which have otherwise been associated with such diseases.[14 15] One study found an association between restricted growth in late gestation and an increased rate of later development of an atopic phenotype, whereas another found contrasting results.[16 17] Similarly, anthropometric measures pointing to growth that is slower than normal in the prepubertal period, such as low adult leg length, leg : trunk ratio and total height, have been linked to higher rates of coronary heart disease, diabetes and mortality, although to lower rates of non-smoking-related cancers.[18–23]

As a proxy for different patterns of imbalanced growth throughout childhood, we considered constructing a measure that would assess an individual's attained 'extra height' (positive or negative) compared with the height that could be expected based on the height of their parents. In general, genetic inheritance accounts for around 80% of the variance in height.[24] Thus, the 'extra height' measure could be a sensitive marker of relative growth below or beyond genetic inheritance, and could possibly be used as an indicator of health or the risk of different diseases.

In this paper, we tested the hypothesis that positive values of 'extra height' would be positively associated with allergic rhinoconjunctivitis, atopic dermatitis and atopic sensitisation but inversely associated with non-atopic asthma and non-atopic wheezing. We also tested the consistency of the results by testing the hypothesis that 'extra height' would be inversely associated with ischaemic heart disease (IHD) and mortality, both of which are known to be influenced by an individual's height or that of their parents.[19 25]

METHODS

Study population

The current study took advantage of the previous MONICA (the Danish monitoring trends and determinants of cardiovascular disease) studies that were part of the international WHO coordinated study, MONICA. The Danish MONICA1 was conducted during 1982–1984, whereas MONICA10 was conducted during 1993–1994. For MONICA1, a random sample of 4807 men and women born in 1922, 1932, 1942 or 1952 and living in 1 of 11 municipalities in greater Copenhagen were invited. After exclusion of 226 individuals of non-Danish origin, those eligible for the study were 4581 individuals. The participation rate was 78.8% (n/N= 3608/4581).[26] MONICA10: all of the original 4581 individuals eligible for MONICA1were eligible for invitation to MONICA10 but 451 had either died, emigrated or could not be reached; thus, 4130 were invited. The participation rate was 64.3% (n/N = 2656/4130), as shown in a flowchart in an earlier publication.[27] For the current study, we selected all of the participants from MONICA10 with complete data on their mother's and father's heights, N=1900. We used data from the MONICA10 health examination and self-administered questionnaires, while we used data of IgE seropositivity from the MONICA1 study.

The study was conducted in accordance with the second Helsinki Declaration and written informed content was obtained from all participants.

Definition of the additional height index

The additional height index (AHI) was designed as: An individual's measured height [minus sign] an individual's expected height. It takes both positive and negative values. The concept of an expected height was based on the national growth charts of Danish boys and girls.[28] The calculation of AHI was made as:

$$\begin{aligned}\text{Males} = {} & \text{Measured height} \\ & - ((\text{mother's height} + \text{father's height})/2) \\ & + \text{ADH}) \\ \text{Females} = {} & \text{Measured height} \\ & - ((\text{mother's height} + \text{father's height})/2) \\ & - \text{ADH})\end{aligned}$$

where ADH=average deviated height=((AHM-APHM) +(APHF-AHF))/2, and where AHM=average height males, APHM=average mid-parental height males, AHF=average height females, and APHF=average mid-parental height females. Thus, ADH is the average that men are higher than their parents plus the average that women are lower than their parents divided by two.

The formula for ADH minimises the effect of statistical fluctuations in height of the parents between the group of males and females. Several alternatives for the calculation of AHI and ADH are elaborated in the online supplementary material.

Physical examination and blood tests

Height and weight of the study participants were measured by the study nurses with participants wearing light clothes and no shoes. The heights of the parents were reported by the study participants. Body mass index (BMI) was calculated. Blood pressure was measured twice with the study participants sitting after 5 min rest and the average calculated. Atopy was defined as a qualitative detection of IgE antibodies specific to 19 common inhalant allergens in serum using the ADVIA Centaur

Allergy Screen Assay, as described previously.[29] Total cholesterol, high-density lipoprotein and triglycerides were measured by enzymatic procedures (Roche, Mannheim, Germany), as described previously.[30]

Self-administered questionnaire from MONICA10

The self-administered questionnaire included information on lifestyle habits, medical history, sociodemographic variables and other potential confounders.

Symptoms of allergic rhinoconjunctivitis were defined as positive answers to all of the following questions: 'have you had itching or stinging from the eyes?', 'have you had itching or stinging from the nose?', and 'have you had a running nose without having a cold within the last 12 months?' Atopic dermatitis was defined as a positive answer to 'has a physician ever told you that you have atopic dermatitis?' Asthma was defined as positive answers to both 'has a physician ever told you that you have asthma?' and 'have you had an attack of asthma within the last 12 months?' Wheezing was defined as positive answers to: 'have you been wheezing within the last 12 months?', and 'have you been woken up by wheezing or whistling in the chest?' Non-atopic asthma and wheezing were defined as asthma/wheezing in individuals without atopy.

Educational level was categorised in four groups (none, low, medium and high) ranging from no vocational qualifications apart from primary and secondary school to >4 years of theoretical education following high school. The average weekly alcohol intake was categorised in five groups as 0, 1–7, >7–14, >14–21, >21 standard drinks (approximately 1.5 cl or 12 g ethanol) per week. Leisure time physical activity was reported as sedentary, light, moderate and vigorous. Smoking status was categorised as never-smoker, ex-smoker or current smoker at <15, ≥15–25 or ≥25 g of tobacco or cigarettes/day, respectively.

Registry-based diagnosis of IHD and mortality due to IHD

From the Danish National Patient Register,[31] including all patients admitted to hospitals in Denmark, and from the Danish Registry of Causes of Death,[32] we obtained information of an individual's first diagnosis of IHD in a hospital and/or death caused by IHD as the primary cause, respectively. The included diagnoses from International Classification of Diseases (ICD), Eighth Revision (ICD8) were 410–414 and from ICD10 were I20–25 in both registers. Denmark never used ICD9. The outcomes used in the paper were: IHD event (participant still alive), death by IHD, and IHD-all (IHD event and/or death by IHD). Participants were followed until 31 October 2012.

Statistics

Statistical analyses were performed using the R-statistical package, V.2.13.0 (http://www.r-project.org/). All p values were two tailed and statistical significance was defined as p<0.05. p Values of likelihood ratio tests were used to test for the significance of all multivariate analyses.

Initially, we divided the population into three equally sized groups (in the following referred to as 'tertiles') with low, medium or high values of additional height (table 2). We used χ^2 tests for trend to examine differences between these three groups with respect to the prevalence of atopic sensitisation, allergic rhinoconjunctivitis, atopic dermatitis, asthma, wheeze, IHD and IHD mortality.

We used logistic regression to model non-atopic asthma, non-atopic wheezing, atopic sensitisation, allergic rhinoconjunctivitis and atopic dermatitis (figures 2 and 3). We did not model atopic asthma/wheeze because of the few participants in these categories. We checked for non-linear associations between all explanatory variables and logit of the dichotomous outcomes using P-splines within the generalised additive model (R 'mgcv' package). We used Cox regression models with age as the underlying time to analyse events of IHD and IHD mortality (figures 2 and 3). We checked the fit of the models by plotting pseudoresiduals against covariate values.[33] Assumptions of linearity were obtained in all logistic regression and Cox regression models. Thus, the estimates of these models (figures 2 and 3) can be interpreted as the increased (or decreased) risk of a health outcome with every one SD increase of AHI.

We performed all analyses with and without BMI to investigate whether part of the effect of AHI seemed to be mediated by BMI; we also tested for possible interactions between BMI and AHI. We then performed all analyses with and without height and weight separately to investigate whether part of the effect of AHI seemed to be mediated by either height or weight alone. Finally, we repeated all analyses with and without 'the educational level' (our best measure of socioeconomic position) of the participants to investigate whether the educational level could account for the effect of AHI.

Sensitivity analyses included repeated analyses in the different strata of age groups and analyses without the highest and lowest percentiles of explanatory variables. Further, we repeated all analyses with AHI with incorporated corrections for secular changes in height and for regression to the mean effects.

RESULTS

The distribution of additional height is given in figure 1. The mean additional height was 0.90 cm (SD=5.71 cm), meaning that the mean attained height of the participants was approximately 1 cm higher than expected from the height of their parents alone but with some variance between study participants. The characteristics of the study population are given in table 1 along with the level of AHI for each characteristic. AHI had significantly different levels in groups of most available characteristics/confounders (table 1). There was no difference between individuals with and without complete

Table 1 Characteristics of the study population and level of additional height index

Characteristics (n missing)	Percentage of all (n group)	Level of AHI (cm) Mean	SD	p Value*,†
Age and gender				
41	30.3 (576)	2.68	5.61	
51	29.5 (560)	1.16	5.61	
61	24.7 (469)	0.11	5.61	
71	15.5 (295)	−1.81	5.61	<0.001
Males	51.4 (977)	0.90	5.88	
Females	48.6 (923)	0.90	5.53	0.003
Body mass index				
<18.5 (kg/m^2)	0.7 (14)	0.48	5.45	
≥18.5 to <25 (kg/m^2)	46.1 (875)	1.06	5.81	
≥25 to <30 (kg/m^2)	38.5 (732)	1.07	5.70	
≥30 (kg/m^2)	14.7 (279)	−0.03	5.36	<0.001
Smoking				
Current	45.3 (859)	0.93	5.77	
Former	27.8 (527)	0.76	5.76	
Never	26.9 (510)	1.01	5.57	0.032†
Alcohol (10)				
None	12.9 (243)	0.37	5.67	
≦14 units/week	63.1 (1193)	0.83	5.71	
>14 units/week	24 (454)	1.39	5.75	0.109†
Vocational training				
Level 1	19.6 (373)	−0.26	5.87	
Level 2	56.1 (1066)	0.92	5.67	
Level 3	19 (360)	1.71	5.58	
Level 4	5.3 (101)	2.06	5.31	0.132†
Physical activity leisure time (24)				
Sedentary	20.6 (387)	0.61	5.45	
Walking	56.2 (1054)	0.92	5.76	
Active/competition	23.2 (435)	1.16	5.86	<0.001
Allergic sensitisation‡ (171)				
Not present	80.8 (1397)	0.91	5.78	
Present	19.2 (332)	1.41	5.49	<0.001
Atopic dermatitis (4)				
Not present	97.5 (1849)	0.88	5.73	
Present	2.5 (47)	1.72	5.06	<0.001
Allergic rhinoconjunctivitis (14)				
Not present	95.1 (1793)	0.89	5.72	
Present	4.9 (93)	1.57	5.56	<0.001
Wheezing (7)				
Present no allergies	3 (56)	−1.31	5.33	
Not present	96.5 (1827)	−0.76	5.80	
Present and allergies present	0.5 (10)	2.36	7.58	<0.001
Physician diagn. Asthma (6)				
Present no allergies	1.9 (36)	−2.58	5.59	
Not present	97.2 (1841)	−1.33	6.17	
Present and allergies present	0.9 (16)	1.81	6.56	<0.001
IHD event (46)				
Not present	89.8 (1665)	1.08	5.76	
Present	10.2 (189)	0.12	5.09	0.083
IHD death (46)				
Not present	88.7 (1645)	0.98	5.71	
Present	11.3 (209)	−1.39	5.36	0.310

p Value obtained by:
*χ^2 test or
†χ^2 test for trend.
‡Positive test to ADIVIA Centaur Allergy Screen.[29]
AHI, additional height index; *diagn.,* diagnosed; IHD, ischaemic heart disease

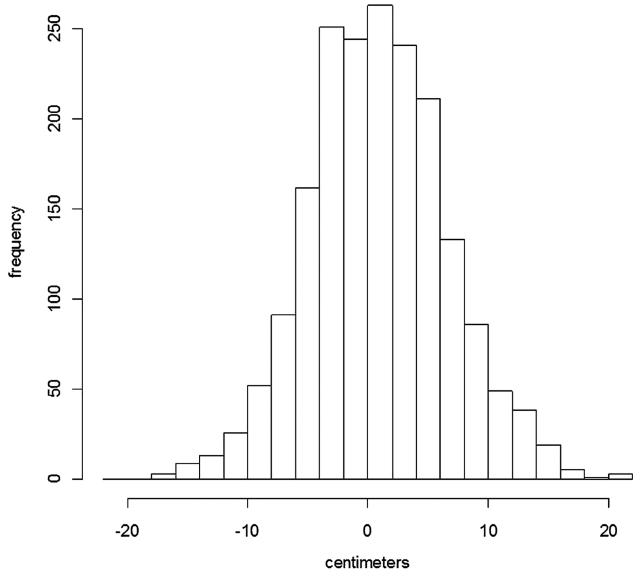

Figure 1 The distribution of the additional height index (measured height–expected height) in a general population of Danish adults, n=1900.

data on mother's and father's height with respect to other variables, such as age, gender, BMI or any of the modelled outcomes. Sensitivity analyses did not change the pattern of results presented below.

The mean level of AHI was higher among individuals with atopic sensitisation, atopic dermatitis and allergic rhinoconjunctivitis than among individuals without (table 1). Also, the mean level of AHI was higher among individuals with atopic asthma/wheeze than among those without (table 1). Further, higher prevalences of atopic sensitisation, allergic rhinoconjunctivitis and atopic dermatitis were recorded among participants within the highest tertile of AHI compared with within

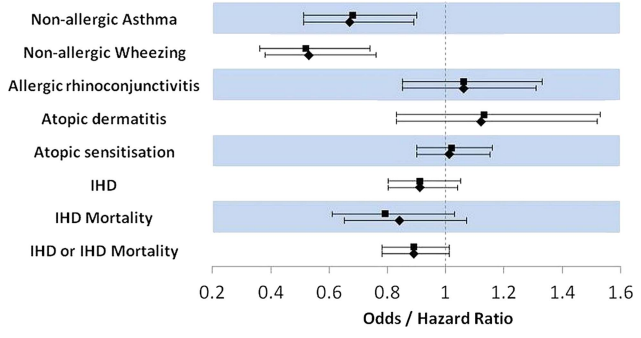

Figure 2 The association of the additional height index (1 SD) with eight health outcomes. OR or HR (ischaemic heart disease (IHD), IHD mortality) with error bars indicate the CIs of the estimates. Diamonds, adjusted for age and gender; squares, additionally adjusted for body mass index, educational level, smoking status, alcohol consumption and physical activity during leisure time. Adjustment of the IHD models also includes serum levels of triglycerides, low-density lipoprotein, high-density lipoprotein and systolic blood pressure.

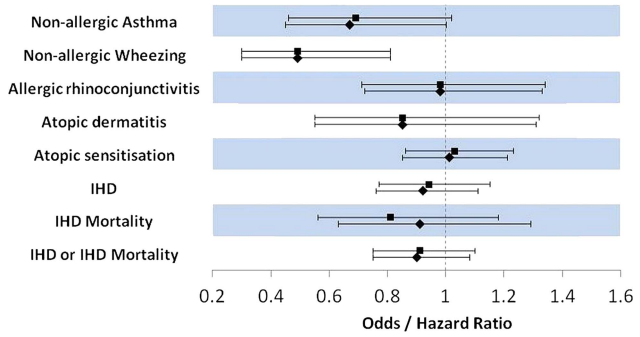

Figure 3 The association of height (1 SD) with eight health outcomes. OR or HR (ischaemic heart disease (IHD), IHD mortality) with error bars indicate the CIs of the estimates. Diamonds, adjusted for age and gender; squares, additionally adjusted for body mass index, educational level, smoking status, alcohol consumption and leisure time physical activity. Adjustment of the IHD models also includes serum levels of triglycerides, low-density lipoprotein, high-density lipoprotein and systolic blood pressure.

the lowest tertile, but this was not statistically significant (table 2). Neither did the regression analyses confirm the associations of AHI with either allergic rhinoconjunctivitis or atopic dermatitis alone (figure 2), but the OR for having either allergic rhinoconjunctivitis or atopic dermatitis was 1.44 (0.84 to 2.44) for one SD increase in AHI.

In contrast, the prevalence of non-atopic asthma/wheeze, IHD and IHD mortality decreased significantly through increasing tertiles of AHI (table 2). Further, in regression analyses, we found significant inverse associations of increasing levels of AHI with non-atopic asthma/wheeze, and inverse associations close to a 5% significance level with IHD/IHD mortality (figure 2, squares). The associations of AHI and these health outcomes were not attenuated by adjustment with potential confounders (figure 2, diamonds). In the case of non-atopic asthma, the adjusted OR is 0.54 (0.38 to 0.77) per one SD of AHI (figure 2). This means that for individuals 5.7 cm (1 SD) taller than expected based on the height of the parents, the odds of having non-atopic asthma is reduced by approximately 46% compared with individuals with the expected height. Thus, our results suggest that for every 5.7 cm increase of AHI, the probability of having non-atopic asthma is approximately halved. Adjustment with weight did not change the associations (data not shown), and there were no interactions or trends towards interactions between AHI and gender (data not shown).

Mid-parental height and parents' height as separate variables were not associated with the outcomes (data not shown). However, to some extent, the study participants' own height resembled the results obtained for AHI (figure 3), as the most noticeable difference was the generally broader CI for height. Results obtained with alternative calculations of AHI are presented in the online supplementary material.

Table 2 Frequencies of diseases in three groups of the additional height index

Level of the additional height index	Low		Middle		High		p Value
	Per cent	(n/N)	Per cent	(n/N)	Per cent	(n/N)	
History of atopic dermatitis	1.58	(10/633)	3.17	(20/631)	2.69	(17/632)	0.204
Symptoms of allergic rhinoconjunctivitis	3.66	(23/629)	5.11	(32/626)	6.02	(38/631)	0.093
Allergic sensitisation*	18.20	(102/564)	18.01	(107/573)	21.32	(123/592)	0.243
All wheezing	4.74	(30/633)	3.17	(20/630)	2.54	(16/630)	0.033
Non-atopic wheezing	4.14	(26/628)	3.05	(19/623)	1.75	(11/630)	0.013
Allergic wheezing	0.64	(4/629)	0.16	(1/626)	0.79	(5/629)	NA
All physician diagnosed asthma	4.11	(26/632)	2.69	(17/631)	1.58	(10/631)	0.002
Non-allergic physician diagnosed asthma	3.03	(19/628)	2.08	(13/624)	0.64	(4/629)	0.001
Allergic physician diagnosed asthma	0.95	(6/629)	0.64	(4/626)	0.95	(6/631)	NA
IHD	14.87	(91/612)	13.13	(81/617)	10.56	(66/625)	0.036
Death IHD	4.89	(31/634)	3.48	(22/633)	1.74	(11/633)	0.005
IHD or death IHD	16.83	(103/612)	14.26	(88/617)	11.20	(70/625)	0.007

p Value obtained by χ^2 test for trend.
*Positive test to ADIVIA Centaur Allergy Screen.[29]
IHD, ischaemic heart disease; NA, not available

DISCUSSION

We created the AHI that we propose reflects health circumstances in childhood independent of the inherited height. We found higher levels of additional height among individuals with atopic sensitisation, allergic rhinoconjunctivitis and atopic dermatitis, but we could not confirm this in adjusted regression analyses. However, we found significant inverse associations of AHI with non-atopic asthma/wheezing and inverse associations with IHD/IHD mortality close to a 5% significance level. The associations with IHD are in line with earlier findings of associations between growth measures and coronary heart disease, mortality, type 2 diabetes and insulin resistance in different ethnic groups and lend support to AHI as an indicator of childhood health.[18–20 22 23]

We speculated that health-focused behaviour in affluent societies could present a supplementary explanation of the increased prevalence of allergic conditions otherwise explained by hygiene and fewer infections. Health focus could lead to changes in dietary patterns and nutritional intake that would again be reflected by changed growth patterns both prenatally and postnatally. Thus, we speculated that increased growth could basically reflect a slightly different construction of organs, cell regulatory mechanisms and function of the immune system that would again lead to a different risk set of several health outcomes, for example, higher risk of allergic conditions and some cancers but lower risks of CVDs. However, increased growth could also reflect lower exposure to infections prenatally and postnatally, and our observations are thus not incompatible with the hygiene hypothesis.

We find some support for our speculations: prenatally, one study found that mothers' changed intake of fatty acids from fish to fatty acids from plants may increase the risk of atopy but possible changes in growth were not recorded.[34] Similarly, another study indicated that poor fetal growth may reduce the risk of skin prick test reactivity during childhood.[17] Considering the childhood period, decreasing risks of asthma, rhinitis and allergic sensitisation in 4-year-old children have been found with increasing socioeconomic position, something that may influence dietary patterns.[35] Finally, changes on a population level, such as decreased stunting in Brazil during fairly similar decades of increases of allergic health outcomes,[4 36] do not contradict our hypotheses. For the same time period, there is some evidence that increased growth may be associated with increased risk of non-smoking-related cancers.[10] Prenatal growth parameters such as birth weight and head circumference have been associated with several childhood cancers in Nordic populations born from 1967.[37] Thus, these findings relate to a period of increasing wealth of Nordic societies, especially of Finland. Further, in a Danish population including participants born between 1930 and 1989, late childhood growth has been associated with thyroid cancer,[38] and early adolescence growth with prostate cancer.[39] These long-term risk sets are complex and the underlying pathways leading to growth, cancer risk and possibly other health outcomes such as allergic conditions are unknown, although insulin-like growth factor levels, overall energy intake and nutritional supplementations have been mentioned.[40 41]

On an overall level, we speculate that a balance between healthy growth and adaptive mechanisms to less optimal conditions could be 'tipped to the healthy side' in allergic diseases. Few periods of relative starvation (skipping meals), which modern and affluent parents tend to avoid but were more common before the 20th century's increase in living standards, could lead to 'less resistance' of the child, for instance via a different set of intestinal microbes,[42] and subsequent to allergies. One study hypothesised that alternate day calorie restriction decreases asthma and seasonal allergies, among other disorders,[43] while another study

found that reduced calorie intake could reduce symptoms in atopic dermatitis.[44] Thus, when some studies indicate an effect of hygiene standards or sibship size to the development of allergic disease with fewer allergies among those born last,[8] we speculate that parents may have been more observant of, for example, nutrients and feeding of their oldest children. However, our results could only partly support these ideas.

AHI was inversely associated with asthma/wheeze among IgE-negative individuals. In this way, our results are in line with other studies defining a separate entity of asthma not responding to corticosteroid treatment,[45] driven by neutrophils,[46] associated with obesity[47] and with onset in adulthood.[45] With the present paper, we further suggest that this entity of non-atopic asthma more commonly occurs in individuals with less optimal health and growth during childhood. A possible explanation for this finding is that reduced airway calibre along with overall reduced growth leads to increased susceptibility to asthma and wheeze. However, a supplementary association between less optimal childhood conditions and late-onset disease cannot be excluded and would correspond to the tendency of an inverse association of growth with risk of IHD that we also observed in this study. In accordance, one study found an inverse association between increasing height and adult-onset asthma,[48] and another found more asthma symptoms within the past 12 months specifically among adults in deprived areas.[49] It is well documented that steroid inhalation therapy for asthma leads to restricted growth and lower adult height.[50] However, the participants in our study were children before the introduction of steroid inhalation therapy in Denmark in the 1980s, and thus we do not think that our results are affected by reduced height due to steroid inhalation therapy. Even though adiposity was a potential confounder, our results were robust to adjustments for BMI/weight; thus, we consider it unlikely that the effect of AHI was simply mediated through adiposity.

The concept of AHI was constructed for the purpose of this study. Therefore, we made an indirect validation of the concept by finding expected inverse associations between AHI and IHD. Further, to test the robustness of the concept, we calculated AHI in three slightly different ways to account for secular changes in height alone and secular changes in height difference between males and females (see online supplementary material), and all three methods subsequently gave essentially similar associations with the health outcomes presented in this paper. Further, we estimated and adjusted AHI for possible regression to the mean effect in heights. We found that even this adjustment did not alter the results presented. Therefore, the idea of AHI seems robust. Further, AHI most likely has the advantage over ordinary height in that it more accurately measures growth of individuals who are, for example, tall but were supposed to be slightly taller. In this case, AHI will assign a slight negative value, whereas ordinary height simply measures 'tallness' (a positive value). Opposite is the case for short individuals. This may be the exact reason for the more tight CIs of the analyses of AHI (figure 2) as compared with height (figure 3) in our study. We tested the association of mid-parental height and parents' height separately with the outcomes, but we did not find associations, as have been reported in other studies.[25 51]

The limitations of the study include possible selection bias. First, individuals were lost to follow-up between MONICA1 and MONICA10. Second, among those actually invited for MONICA10, some chose not to participate. We cannot exclude that they may have chosen not to participate due to causes related to exposure and outcomes of the study. This may also have had an impact on the generalisability of the study. However, in respect of the registry-based outcomes, we had no loss to follow-up with regard to mortality and incidence of CVD. The definitions of allergic rhinoconjunctivitis, atopic dermatitis, asthma and wheezing all came from questionnaires and may have been subject to recall bias or misclassification. Educational level was the best measure of social class, and residual confounding could in theory have caused the associations found. However, most of these methodological shortcomings would likely have led to attenuation of the estimates, and yet we found results that were consistent with the literature (IHD) and differences between atopic asthma/wheezing and non-atopic asthma/wheezing.

In conclusion, we propose AHI as a measure that reflects living circumstances mainly in infancy, childhood and adolescence and suggest that the level of attained additional height may indicate the chance of certain health or disease outcomes during adult life. We speculate that allergic conditions, in contrast to non-atopic asthma, wheeze and IHD, are associated with healthy living during childhood.

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Methods for calculating Additional Height Index

Additional Height Index (AHI) is defined for each participant as

AHI = Height – Mid parental height -/+ ADH

where the – sign is used for males and the + sign is used for females.

and where we have defined expected/Average Deviated Height as

ADH = (Expected male height – Expected female height)/2

We are aware that the difference in expected height between males and females can vary across time, culture and countries.

In the following we will explain three different methods for calculating AHI (method 1-3), which are really just variations of calculating ADH. Further, we show that the estimates of the associations of AHI with the health outcomes in the study asthma etc are independent of the particular choice of calculating AHI.

We are also aware that regression to the mean in height could affect AHI. In the current study we do not correct for the regression to the mean effect. In the following, however, we give an example of how to quantify the regression to the mean effect (method A1), and show that correcting for regression to the mean effect does not change the estimates of the associations of AHI with the health outcomes significantly.

Method 1) for calculating AHI

According to method 1) AHI is calculated as specified above and corresponds to the method used in the paper. However, the exact method of calculating ADH can be specified:

From our dataset we have calculated the Average of the Height of Male participants (AHM) and the Average of the Height of Female participants (AHF). To make these estimates more exact, ie to avoid the effect of statistical fluctuations of the height of the parents, we correct these estimates by the average of the mid parental height for the two groups, males and females. That is, we calculated the Average mid Parental Height for Male participants (APHM) and the Average mid Parental Height for Female participants (APHF). Ie the estimated mean of the height difference between males and females were calculated as

ADH = ((AHM-APHM) - (AHF-APHF))/2

= ((AHM-APHM) + (APHF-AHF))/2

Ie the average that men are higher than their parents + the average that women are lower than their parents divided by two.

From our dataset we have ADH=5.84cm

AHM-APHM = 12.31cm

AHF-APHF = 0.63cm

Method 2) for calculating AHI

As mentioned above ADH can vary over time due to e.g. changes in the traditions for the upbringing of boys and girls. This may be relevant for in our study since we have participants from four age strata. Thus, we have calculated ADH for each age strata separately and four separate estimates of ADH were used in the formula for each of the four age groups (40, 50, 60 and 70 years).

In our dataset we have:

ADH_{40} = 6.00cm, ADH_{50} = 6.05cm, ADH_{60} = 5.55cm, ADH_{70} = 6.14cm

Method 3) for calculating AHI

In Danish hospitals ADH is assumed to be 6.5cm. Hence an alternative method for calculating AHI is to assume ADH to be 6.5cm.

Method A1) for calculating AHI

This is like method 1) except that we make a correction for regression to the mean. If the parents of a participant were unusual high then we would expect this to be caused by several circumstances which not all are inherited to the participants. We would therefore expect a negative relationship between AHI and mid parental height. In figure 1 the AHI calculated via method 1) is plotted against mid parental height. The best fit line has a negative slope in correspondence with the regression to the mean effect. In figure 2 the points have been tilted (described below) such that the slope is zero and thereby the supposed regression to the mean effect has been removed. If we assume that the slope of the points in figure 1 is solely due to the regression to the mean effect then we can remove this effect by tilting the values of AHI for each participant according to this equation:

$AHI_4 = AHI_1 - \text{intercept} - \text{slope} * \text{MidParentalHeight}$

Where intercept and slope is from the best fit line in figure 1.

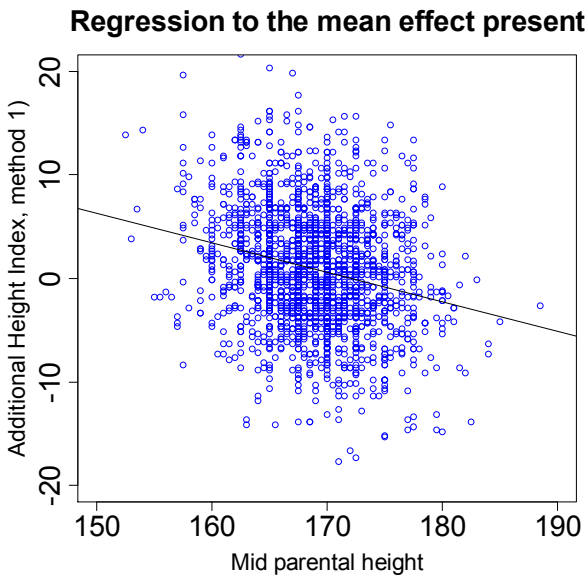

Figure 1 Scatterplot of AHI_1 from method 1) and mid parental height. One blue circle for each participant. The best fit line could be caused by regression to the mean.

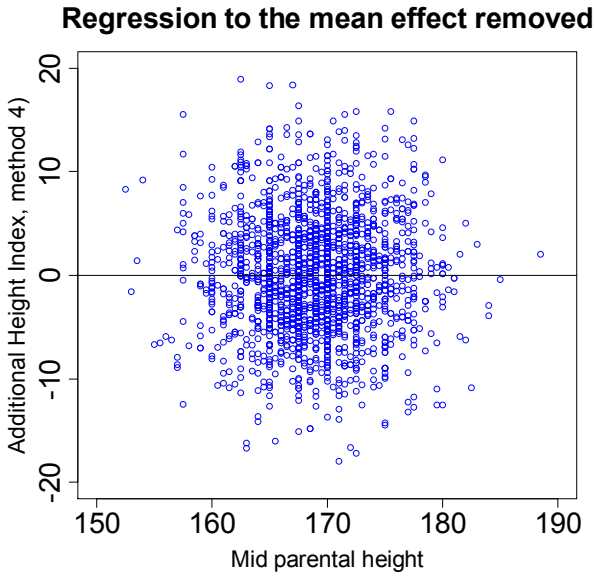

Figure 2 Scatterplot of AHI_4 from method A1) and mid parental height. One blue circle for each participant. As the consequence of the construction method of AHI_4 then the best fit line has zero slope.

Similar corrections of the AHI according to method 2) and 3) could also be done.

Results obtained with the different methods for calculating Additional Height Index

In this section, we present results of the regression analyses (corresponding to Figure 2 of the paper) when AHI is calculated by the methods 1), 2), 3), A1):

The association of the Additional Height Index (AHI) by four methods with eight health outcomes. Results are given as OR (Odds Ratio) or as HR (Hazard Ratio) for one standard deviation increase of the Additional Height Index

	Method 1) *	**Method 2)**	**Method 3)**	**Method A1)**
	OR per sd AHI	**OR per sd AHI**	**OR per sd AHI**	**OR per sd AHI**
Non-allergic asthma	0.54 (0.38-0.77)	0.53 (0.37-0.76)	0.54 (0.38-0.77)	0.52 (0.36-0.75)
Non-allergic wheezing	0.69 (0.52-0.91)	0.69 (0.52-0.91)	0.69 (0.51-0.91)	0.69 (0.51-0.92)
Allergic rhinoconjuntivitis	1.05 (0.84-1.31)	1.04 (0.83-1.30)	1.05 (0.84-1.31)	1.01 (0.81-1.27)
Atopic dermatitis	1.10 (0.8-1.49)	1.10 (0.81-1.49)	1.10 (0.81-1.49)	1.02 (0.74-1.39)
Atopic sensitisation	1.02 (0.89-1.15)	1.02 (0.90-1.15)	1.02 (0.89-1.15)	1.02 (0.89-1.16)
	HR per sd AHI	**HR per sd AHI**	**HR per sd AHI**	**HR per sd AHI**
IHD	0.91 (0.80-1.05)	0.91 (0.79-1.04)	0.91 (0.79-1.05)	0.92 (0.80-1.06)
IHD mortality	0.79 (0.61-1.03)	0.80 (0.61-1.04)	0.79 (0.61-1.03)	0.80 (0.61-1.05)
IHD or IHD mortality	0.89 (0.78-1.01)	0.89 (0.78-1.01)	0.89 (0.78-1.01)	0.89 (0.78-1.02)

*Corresponds exactly to results given in Figure 2

The estimates are adjusted for age, gender, body mass index, educational level, smoking status, alcohol consumption, physical activity during leisure time. The IHD models are additionally adjusted for serum levels of Triglycerides, LDL, and HDL, and for systolic blood pressure