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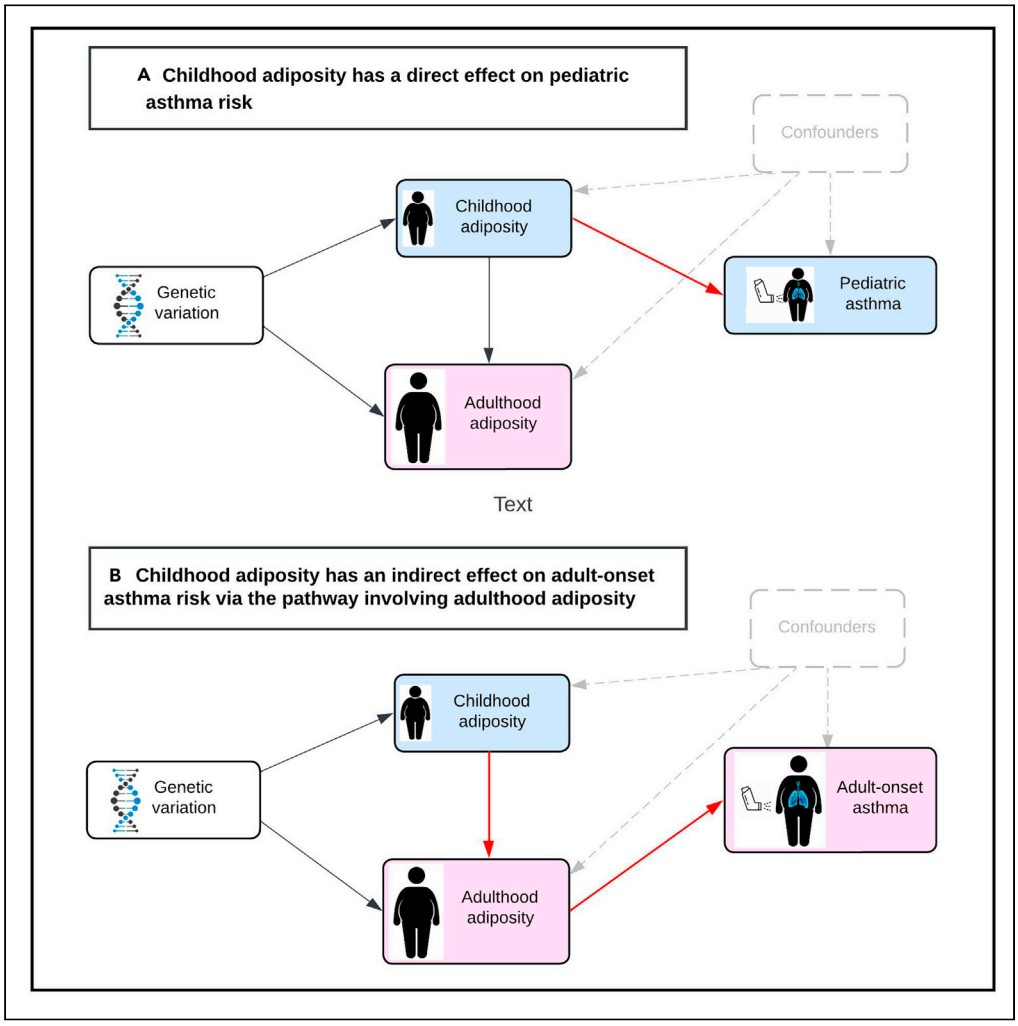

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Highlights

Adiposity is a known risk factor for asthma

Cases of asthma can be diagnosed at various timepoints throughout the lifecourse

We used human genetics to disentangle lifecourse effects of adiposity on asthma risk

Evidence suggested that childhood adiposity directly increases risk of pediatric asthma

Independent of this effect, adulthood adiposity increased risk of adult-onset asthma

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A lifecourse Mendelian randomization study uncovers age-dependent effects of adiposity on asthma risk

Helena Urquijo,[1,2] Genevieve M. Leyden,[1,2] George Davey Smith,[1] and Tom G. Richardson[1,3,*]

SUMMARY

Evaluating the long-term consequences of childhood lifestyle factors on asthma risk can be exceptionally challenging in epidemiology given that cases are typically diagnosed at various timepoints throughout the lifecourse. In this study, we used human genetic data to evaluate the effects of childhood and adulthood adiposity on risk of pediatric (n = 13,962 cases) and adult-onset asthma (n = 26,582 cases) with a common set of controls (n = 300,671) using a technique known as lifecourse Mendelian randomization. We found that childhood adiposity directly increases risk of pediatric asthma (OR = 1.20, 95% CI = 1.03–1.37, p = 0.03), but limited evidence that it has an effect on adult-onset asthma after accounting for adiposity during adulthood (OR = 1.05, 95% CI = 0.93–1.17, p = 0.39). Conversely, there was strong evidence that adulthood adiposity increases asthma risk in midlife (OR = 1.37, 95% CI = 1.28–1.46, P = 7×10^{-12}). These findings suggest that childhood and adulthood adiposity are independent risk factors for asthma at each of their corresponding timepoints in the lifecourse.

INTRODUCTION

Pediatric asthma is the most common type of chronic disease among children which substantially contributes to the increasing global prevalence of asthma anticipated to affect 400 million individuals by 2025. One of the postulated explanations for this rise in cases is the escalating prevalence of childhood obesity, which has been reported to increase asthma risk based on findings from multiple study designs.[1] However, establishing robust evidence of causal effects between risk factors and disease is notoriously challenging in a conventional epidemiological setting due to the influence of confounding factors and reverse causation. This is the motivation behind Mendelian randomization (MR), a causal inference technique which harnesses genetic variants quasi-randomly dispersed throughout a population to more reliably separate causal from merely correlated risk factors.[2,3] That said, MR studies are often interpreted as 'lifelong' effects which presents a limitation in terms of interpreting causal relationships which may vary over the lifecourse, such as the effect of childhood adiposity on risk of asthma onset during childhood and later life.

We recently extended the principles of MR to investigate causal relationships which may vary throughout the lifecourse using genetic variants with time-varying effects.[4,5] For example, this approach previously found evidence that being overweight in childhood directly increases risk of type 1 diabetes, whereas the influence of adiposity on type 2 diabetes risk is largely attributed to a long-term and sustained effect of remaining overweight for many years over the lifecourse.[6] In this current study, we sought to evaluate the effects of childhood and adult adiposity on asthma risk based on cases with recorded onset at two separate stages in life using data from the UK Biobank (UKB) study.[7]

RESULTS

The derivation and validation of our genetic instruments for childhood and adult adiposity have been described in detail previously.[4,8–10] These consisted of 313 independent genetic variants robustly associated (i.e., $P < 5 \times 10^{-8}$) with childhood adiposity and 580 independent genetic variants robustly associated with adult adiposity. Genetic estimates on pediatric- (i.e., diagnosed before or at 19 years of age) and adult-onset asthma (i.e., diagnosed between ages 20 to 60 years) were obtained from a previously undertaken genome-wide association study (GWAS).[7] This study consisted of 13,962 pediatric asthma cases and 26,582 adult-onset asthma cases with a common set of 300,671 controls all based on participants from the UKB study.

First, we found evidence that childhood adiposity increases risk of childhood-onset asthma based on the inverse variance weighted (IVW) method (Odds Ratio (OR) = 1.20, 95% Confidence Interval (CI) = 1.03 to 1.37, p = 0.03). Similar effect estimates using alternative MR approaches supported these findings (Figure 1A). In contrast, there was weak evidence that genetically predicted adulthood adiposity has

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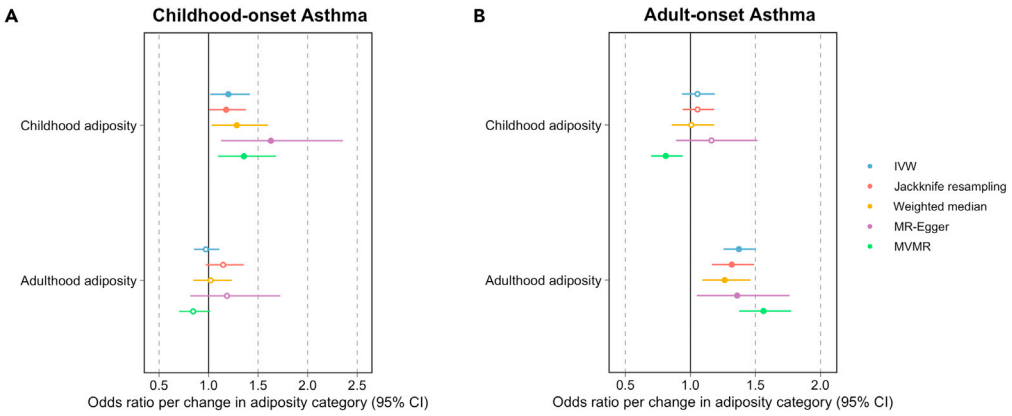

Figure 1. Forest plots depicting lifecourse effects of adiposity on asthma risk

(A and B) Forest plots illustrating lifecourse Mendelian randomization estimates of childhood and adulthood adiposity on (A) childhood-onset and (B) adult-onset asthma risk. IVW, inverse variance weighted method; MVMR, multivariable Mendelian randomization estimates. Adiposity categories are based on the UK Biobank field 1687 where participants were asked whether they were 'thinner', 'about average' or 'plumper' compared to the average at 10 years old.

an effect on childhood-onset asthma risk (e.g., IVW OR = 0.97, 95% CI = 0.84 to 1.10, p = 0.68), providing a proof of concept for lifecourse MR given that in this instance the analyzed outcome occurs earlier in life compared to the measured risk factor. Simultaneously estimating the effects of childhood and adult adiposity on childhood-onset asthma further suggested that being overweight in early life has a direct consequence on asthma risk at this early stage in the lifecourse (OR = 1.36, 95% CI = 1.14 to 1.57, p = 0.005).

Conversely, using data on adulthood-onset asthma provided weak evidence that childhood adiposity has an effect on asthma risk in midlife (e.g., IVW OR = 1.05 95% CI = 0.93 to 1.17, p = 0.39), whereas there was strong evidence that adulthood adiposity has an effect on asthma risk during adulthood (e.g., IVW OR = 1.37, 95% CI = 1.28 to 1.46, $P = 7 \times 10^{-12}$). This finding was supported by multiple MR methods, as well as by estimates derived in a multivariable setting (OR = 1.56, 95% CI = 1.44 to 1.69, $P = 9 \times 10^{-13}$) whilst simultaneously estimating the effect of childhood adiposity (Figure 1B). Estimates derived using jackknife resampling similarly provided concordance evidence of this effect, suggesting that overlapping samples in this study are unlikely to have substantially biased results. Evaluating the reverse direction of effect (i.e., whether liability toward asthma in either childhood or adulthood influences adiposity levels at these timepoints) provided comparatively weaker evidence, most notably based on estimates derived using the MR-Egger method (Childhood: Beta = −0.008, 95% CI = −0.018 to 0.002, p = 0.11, Adulthood: Beta = 0.009, 95% CI = −0.024 to 0.041, p = 0.61).

DISCUSSION

Our findings provide compelling evidence that adiposity in childhood and adulthood are independent risk factors for asthma risk at each of their corresponding timepoints in the lifecourse. A key strength of our lifecourse MR approach is that it is capable of evaluating robust evidence of the direct effects of early life exposures, which would be extremely difficult to undertake without the use of human genetics, given the influence of confounding factors throughout the lifecourse. A proof of principle for this technique is the very limited evidence found in this study that adulthood adiposity has an effect on childhood-onset asthma risk, which is to be expected given that this outcome occurs at an earlier stage in the lifecourse than the exposure.

Applying this approach herein provides evidence that a specific causal effect of adiposity exists during early life on risk of childhood-onset asthma risk, which therefore may develop into a lifelong (and potentially immutable) disease. These results therefore support the hypothesis that one of the possible contributing factors for the rise in prevalence of childhood-onset asthma is the increasing numbers of individuals living with childhood obesity.[11] Findings from our analyses also support those concluded by a recent study which conducted univariable analyses using childhood BMI instruments derived from 39,620 individuals aged between 2 and 10 years.[12] One of the key differences between our study and theirs is that they did not simultaneously estimate the effects of childhood and adult adiposity on asthma risk using an MR approach. As such, their effect estimates must be interpreted as total effects rather than direct and indirect effects as derived using our multivariable MR approach. Instead, the authors of this recent study applied a genomic structural equation model to evaluate whether effects of childhood BMI may be explained (at least in part) by the genetic component of adult BMI.

In conclusion, our findings emphasize the importance of introducing preventative strategies to help address the childhood obesity epidemic. This should help improve the quality of life for patients living with early-onset asthma as well as the many years over the lifecourse that this disease contributes to worldwide healthcare burdens.

Limitations of the study

Our study has noteworthy limitations. Our previously derived childhood adiposity score is based on recall data from the UKB study. Consequently, we have conducted several validation studies of this score as discussed in the STAR methods section to support its application in this

study.[4,8–10] Additionally, we note that the genetic estimates on pedatric- and adult-onset asthma used in this study were derived from two previous GWAS of asthma using cases diagnosed before and after age 20 years in the lifecourse.[7] Future research should therefore further investigate the aetiological relationship between adiposity and asthma risk at more specific timepoints over the lifecourse (e.g., late adolescence and early adulthood) as and when sufficiently powered sample sizes become available.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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AUTHOR CONTRIBUTIONS

H.U., G.M.L., and T.G.R. conducted statistical analyses. All authors contributed to the design of the study and wrote the manuscript. All authors read and approved the final version of the manuscript.

DECLARATION OF INTERESTS

T.G.R. is an employee of GlaxoSmithKline outside of this work. All other authors declare no conflicts of interest.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
TwoSampleMR package	Hemani et al.	Hemani et al.[13]
ggplot2 package	Ginestet et al.	Ginestet et al.[14]
Other		
Summary genetic association data: adiposity	Richardson et al.	Richardson et al.[4]
Summary genetic association data: asthma	Ferreira et al.	Ferreira et al.[7]

RESOURCE AVAILABILITY

Lead contact

Tom G Richardson (tom.g.richardson@bristol.ac.uk).

Materials availability

This study did not generate any new unique reagents.

Data and code availability

Genetic association data were obtained from the various resources listed in the key resources table. This paper does not report original code.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Data on childhood-onset asthma were obtained from a previously conducted GWAS of 13,962 asthma cases diagnosed by a doctor before or at 19 years of age and 300,671 controls in UKB.[7] The same study analyzed 26,582 adult-onset asthma cases diagnosed between the ages of 20–60 years against the same set on controls (referred to as 'adult-onset asthma'). Sex and an indicator of the array used for genotyping were accounted for as covariates in regression models. Sample sizes were restricted to participants of European descent in the UKB. The authors concluded that childhood-onset asthma has a partly distinct genetic architecture compared to asthma that first develops in later life, highlighting differences in the pathophysiology between these disease subtypes.[7]

All individual participant data used in this study were obtained from the UK Biobank (UKB) study, who have obtained ethics approval from the Research Ethics Committee (REC; approval number: 11/NW/0382) and informed consent from all participants enrolled in UKB.

METHOD DETAILS

Instruments for lifecourse Mendelian randomization

Derivation of genetic instruments for childhood and adult adiposity have been described in detail previously.[4] In brief, genome-wide association studies (GWASs) were conducted on 453,169 UKB participants who reported whether they were 'thinner', 'about average' or 'plumper' at age 10 years compared to the average. GWAS on the same sample were conducted based on their measured adult body mass index (mean age: 56.5 years old) which was categorised into the same proportions as the childhood adiposity variable for comparative purposes. In total, there were 313 independent instruments for childhood adiposity and 580 independent instruments for adult adiposity. 92 of the childhood instruments were also genome-wide significant (i.e., $P < 5 \times 10^{-8}$) with adulthood adiposity (29.3%) and 87 of the adult instruments were genome-wide significant for childhood adiposity (15%).

These instrument sets have been extensively validated in three independent cohorts; the Avon Longitudinal Study of Parents and Children (ALSPAC),[4] the Young Finns Study[8] and the Trøndelag Health (HUNT) study[9]). Furthermore, a recent study has found that these childhood genetic instruments much more strongly influence DXA-derived total fat mass during childhood compared to lean mass,[10] supporting their validity as genetic proxies for adiposity rather than simply capturing effects of having a larger body size.

QUANTIFICATION AND STATISTICAL ANALYSIS

We firstly conducted univariable MR to estimate the total effects of childhood adiposity on asthma risk using data from the childhood and adulthood timepoints in turn. These estimates were derived using the inverse variance weighted (IVW) method, which takes SNP-outcome estimates and regresses them on the SNP-exposure associations.[15] The weighted median[16] and MR-Egger[17] were used to assess the robustness of the IVW estimates to horizontal pleiotropy, whereby genetic variants influence multiple traits or disease outcomes via independent biological pathways.[17] Multivariable MR, an extension of MR that employs multiple genetic variants associated with multiple measured risk

factors, was used to calculate the direct and indirect effects of childhood and adulthood adiposity, simultaneously, on asthma risk at both timepoints.[18,19]

The above two-sample approaches all have different underlying assumptions which allows more robust inferences to be made when there is concordance amongst their derived effects estimates. However, given that there are overlapping samples in these analyses given that we wanted to maximise the wealth of data available in UKB, estimates from these approaches may be prone to overfitting bias induced when there are overlapping samples between exposures and outcomes in MR analyses.[20] As such, we additionally applied a jackknife resampling approach to estimate effects (as described previously[20]) to further evaluate the robustness of our estimates. Analyses were conducted using the 'TwoSampleMR' R package. Forest plots in this paper were generated using the R package 'ggplot2'.