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ORIGINAL RESEARCH

Causal effects of time-varying body size on selected autoimmune disorders: a life course Mendelian randomisation study

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ABSTRACT

Background Based on Barker's hypothesis, some studies investigated the associations between birth weight and several disorders. Apart from issues with statistical power and well-known shortcomings of the observational study design, there are no studies accounting for changes in weight-related body size over the life course regarding rheumatoid arthritis, psoriasis, psoriatic arthritis and multiple sclerosis.

Methods Using genetic information of up to 806 834 participants, this study investigated the associations between time-varying weight-related body size from birth to adulthood and the mentioned autoimmune diseases. Performing Mendelian randomisation (MR), the radial inverse-variance weighted approach was used iteratively in primary analyses. Robustness of the results was confirmed in several sensitivity analyses. Potential time-dependent mediation mechanisms were identified through network-clustering and assessed using multivariable MR.

Results Genetically predicted birth weight (fetal effect) was positively associated with rheumatoid arthritis (OR 1.44; 95% CI 1.17 to 1.77; P_{adj} =0.005) but not with psoriasis, psoriatic arthritis or multiple sclerosis. This association was found to be mediated by body mass index (BMI) in adulthood (OR 1.45; 95% CI 1.14 to 1.84; P_{adj} =0.019) rather than childhood. The direct effect of birth weight attenuated (OR 1.19; 95% CI 0.88 to 1.62); P_{adj} =1) after adjustment for time-varying BMI.

Conclusion Increased birth weight appears to be a risk factor for later manifestation of rheumatoid arthritis due to both fetal genetic components and high BMI persisting into adulthood. Approaches to prevent and minimise the risk of rheumatoid arthritis could include preventing obesity in adults with high birth weight.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The development of weight-related body size and its impact on many diseases is thought to vary over the life course.
⇒ Some observational studies investigated the associations between birth weight and autoimmune disorders without distinguishing fetal and maternal genetic components or accounting for changes in body measurements over the life course or other potential confounding and mediation factors.

WHAT THIS STUDY ADDS

⇒ Extending the usual Mendelian randomisation analysis by an iterative approach with focus on outlier assessment as well as performing graphical network clustering, this study investigated the causal effects of time-varying weight-based body size on selected autoimmune diseases considering further confounding and mediation mechanisms.
⇒ This study suggests that the risk of increased birth weight on rheumatoid arthritis is attributable to the fetal rather than maternal genetic component and a high body mass index persisting into adulthood.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The understanding of time-dependent effects and proportion of individual contribution is important for better management and prevention of the often genetically determined risk for related autoimmune diseases.

INTRODUCTION

The fetal origins of disease in adulthood hypothesis, also known as the Barker hypothesis,[1] states that environmental factors acting during pregnancy influence fetal development, thereby increasing susceptibility to certain diseases later in life.[2 3] It is hypothesised that developing organs and systems are more sensitive to environmental influences during certain critical periods of gestation and shortly after birth, resulting in phenotypes that are better adapted to the environment, providing an evolutionary advantage.[4] This programming can lead to impairments in important physiological and metabolic systems that are associated with the subsequent development of chronic diseases.[4] Birth weight is one of the most important determinants of perinatal outcome.[5] A number of large cohort studies reported a consistent

association between low birth weight and increased risk of type 2 diabetes,[6 7] hypertension[8] and cardiovascular disease,[9 10] while larger birth weight was related to an increased risk of obesity.[11] However, the association between birth weight and the development of other adult diseases such as respiratory diseases, psychiatric disorders or cancers came to contradictory results.[12–16] Moreover, birth weight is influenced not only by a variety of lifestyle factors, but also by fetal and maternal genetic determinants that cannot be examined in observational studies.[17] The ability to resolve maternal and fetal genetic contributions to birth weight is important for essential insights into the underlying biological regulation and origins of observational associations.[17]

So far, there are only some investigations on the relationship between birth weight and autoimmune diseases.[18 19] An observational study found a positive association between birth weight and rheumatoid arthritis,[20] while another investigation observed no association between birth weight and multiple sclerosis later in life.[21] Moreover, it is thought that the development of weight-based body size and its impact on many diseases vary over the course on an individual's life time.[22] Thus, it remains unclear, whether and how time-varying body composition is causally related to autoimmune diseases in adulthood. A Mendelian randomisation (MR) approach can strengthen the causal inference by using genetic variants, which are randomly allocated at meiosis, as instrumental variables for an exposure and which are, therefore, independent of factors biasing observational studies. In this study, we performed a two-sample summary data MR analysis to assess the associations of weight-related body size over the entire life course and certain autoimmune diseases, namely rheumatoid arthritis, psoriasis, psoriatic arthritis and multiple sclerosis.

METHODS
Study design
The Mendelian MR design can be used to investigate a causal relationship between a potential exposure and an outcome of interest. The main advantage of this study design is that it overcomes unobserved confounding, which is a fundamental problem of observational studies. Briefly, MR uses genetic variation as a natural randomisation process and in this way mimics a randomised

controlled trial as the gold standard of evidence. In an instrumental variable setting, the summary-level two-sample MR uses summary statistics of genome-wide association studies (GWASs) to test whether a modifiable risk factor affects an outcome. As instruments we used single-nucleotide polymorphisms (SNPs), which can only be considered valid if the following three core assumptions are met. (1) SNPs are strongly associated with the exposure (relevance assumption); (2) there are no common causes between SNPs and the outcome (independence assumption) and (3) SNPs affect the outcome only through the exposure (exclusion restriction assumption). With instrument validity in mind, we embedded the usual MR in an iterative process, focusing on SNPs that violate at least one of the last two assumptions.

Study samples
In this study, we considered birth weight from two perspectives: the birth weight in the context of fetal and maternal genetic effects. Warrington *et al* used structural equation modelling to decompose the contributions of direct fetal and indirect maternal genetic effects across the genome.[17] In this way, we were able to investigate whether a possible association found could be attributed to the fetal or maternal part. Both datasets were derived from the EGG Consortium using additionally the UK Biobank Resource. The underlying meta-analyses processed birth weight information of overall 298 142 newborns.

For the time-varying mediation analysis, we used the body mass index (BMI) as proxy for obesity measured at two time periods, in childhood and adulthood. GWAS for childhood BMI included up to 39 620 children at the age between 2 and 10 years.[23] For adulthood BMI, we used summary level data from a meta-analysis combining up to 806 834 participants from the GIANT consortium and UK Biobank cohort.[24]

As outcomes, we considered the following autoimmune diseases in individuals of European ancestry, which are described in table 1: rheumatoid arthritis, multiple sclerosis, psoriasis and psoriatic arthritis. The rheumatoid arthritis summary statistics arose from a meta-analysis GWAS in 22 European cohorts including 14 361 cases and 43 923 controls.[25] Summary-level data for multiple sclerosis based on a meta-analysis consisting of 15 GWASs included overall 47 429 diagnosed cases and

Table 1 Dataset description of the outcomes used in the Mendelian randomisation analyses

Characteristic	Rheumatoid arthritis	Multiple sclerosis	Psoriasis	Psoriasis arthritis
Cases (abs. (rel.))	14 361 (0.25)	47 429 (0.41)	5621 (0.02)	2063 (0.01)
Controls (abs. (rel.))	43 923 (0.75)	68 374 (0.59)	252 323 (0.98)	252 323 (0.99)
Sample size	58 284	115 803	257 944	254 386
Available SNPs	8 747 963	6 304 359	16 355 286	16 355 281
Reference	Okada *et al*[25]	Patsopoulos *et al*[26]	FinnGen[27]	FinnGen[27]

SNP, single-nucleotide polymorphism.

68 374 controls.[26] Both psoriasis and psoriatic arthritis GWASs were obtained from the FinnGen Consortium and compared 5621 and 2063 cases with 252 323 controls, respectively.[27]

Instrument selection

Where available and not preselected, SNPs with a minor allele frequency (MAF) less than 0.01 and an imputation score less than 0.8 were removed from all datasets as part of the quality control process. If possible, missing information in the datasets was imputed based on the 1000 Genomes reference panel.

To ensure the relevance assumption we considered in a further step all birth weight associated SNPs based on the genome-wide significance threshold $p=5\times10^{-8}$ as potential instruments. Regarding the independence of genetic variants, we applied PLINK clumping with a conservative clumping cut-off $r^2=0.001$ to prune SNPs in linkage disequilibrium. During the harmonisation process, we excluded all palindromic SNPs (ie, MAF>0.42) and searched, if necessary, for proxy-SNPs in the outcome dataset based on $r^2>0.8$.

Statistical analyses

To consider all necessary aspects of the investigated relationships, the statistical analyses in this study consisted of several steps. First, we estimate total effects of birth weight on the selected autoimmune diseases by performing univariable MR analyses. Second, we applied a network-clustering procedure to assess clusters of phenotypes associated with the chosen instruments and thus possibly responsible for horizontal pleiotropy. Third, if any cluster was found distorting notably a total effect, multivariable MR (MVMR) was performed to investigate the potential confounding or mediation mechanism. Besides assessing pleiotropy, this hypothesis-free approach also allowed us to ensure whether a time-dependent effect can indeed be assumed, in which a found association between birth weight and any of the mentioned autoimmune diseases is mediated by BMI later in life. Within each of these steps, we applied a range of sensitivity analyses to ensure the robustness of results.

Total effects

Total effects in terms of univariable associations between genetically predicted birth weight and the mentioned autoimmune diseases were calculated performing the radial inverse variance weighted (IVW) regression with modified second-order weights as the principal analysis method. As long as the MR assumptions are met, this approach has the highest statistical power and otherwise allows the detection of outliers. To evaluate the robustness and consistency of estimates, we applied this approach iteratively. In each iteration step we identified outliers using Cochran's Q-statistic, as a quantitative measure of contribution to global heterogeneity, with $\alpha_Q = 0.01$ as the threshold for classification. In addition, we evaluated and compared the goodness of fit of the first and last

iterations by visually assessing the radial and the funnel plots and also conducted a leave-one-out analysis.

To assess the validity of causal estimates obtained by the radial IVW approach with respect to the plausibility of the non-testable MR assumptions, we performed a range of pleiotropy-robust regression methods, which account for different patterns of pleiotropy, as a part of sensitivity analyses. In this context, the weighted median provides consistent point estimates as long as less than half of the instruments are invalid. The same applies to the weighted mode approach, even when more than 50% of the instruments are invalid. We applied the Robust Adjusted Profile Score to account for weak instrument bias and used the pleiotropy residual sum and outlier (PRESSO) test to identify potential pleiotropy as well as compare the distortion in estimates before and after outlier removal. The CAUSE (causal analysis using summary effect estimates) distinguishes between correlated and uncorrelated pleiotropy and accounts for sample overlap in the GWASs of an exposure and outcome using all available genetic variants. Lastly, we tested the final radial IVW models for directional pleiotropy using the Radial MR-Egger intercept test, and assessed heterogeneity using the Cochran's Q and Ruecker's Q' statistics.

Network clustering

The observed heterogeneity in some of our final models prompted us to investigate whether there are traits responsible for horizontal pleiotropy, and accordingly, for potential biases in the effect estimates. Therefore, we conducted a PhenoScanner[28 29] search for all known phenotypes associated with the instruments used in our analyses. In the next step, we clustered the results using a graphical network analysis, with the goal of finding groups of related traits rather than single phenotypes (eg, cardiovascular diseases rather than hypertension or myocardial infarction). Finally, for each cluster we excluded the cluster-specific SNPs and reran the MR analyses.

Time-varying mediation analysis

Since the analyses from our network clustering approach revealed evidence that one association found was mediated by obesity (and metabolism), but the effect of weight-based body size on many outcomes is likely to vary over time, we examined the magnitude of this time-varying mediation effect in more detail.[30] Thus, we decomposed in a MVMR the respective estimated total effect into a direct effect, which can be attributed directly to birth weight, and an indirect effect, which can be attributed to BMI that is allowed to vary over time (figure 1). In the multivariable setting, we performed the robust IVW approach with multiplicative random effects as the main analysis and the modified IVW, random effects MR-Egger, median and MR-Lasso methods as sensitivity analyses. The latter approach uses the multivariable IVW regression after omitting invalid genetic variants. Analogously to the univariable case, we quantified heterogeneity by calculating the exposure-outcome-specific Q statistics,
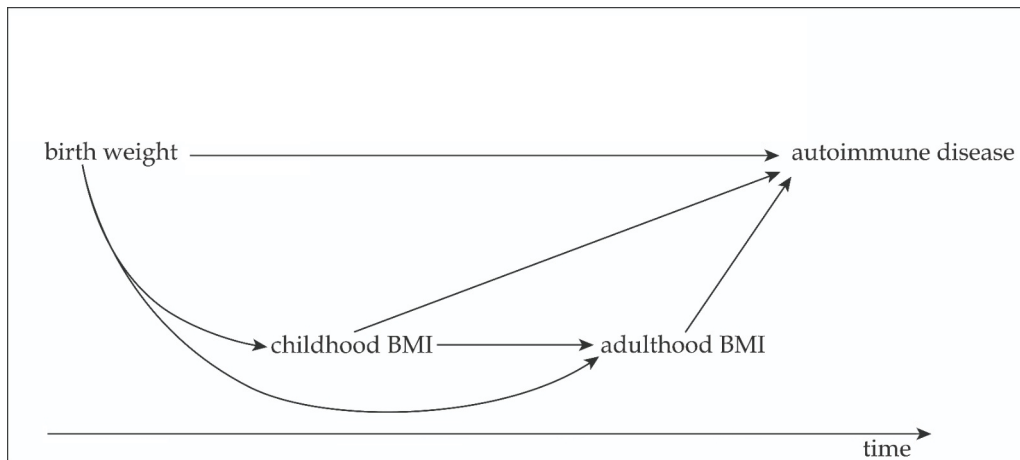
Figure 1 Simplified illustration of the setting in Mendelian randomisation analysis considering time-varying mediation effects of BMI. BMI, body mass index.

whereas directed pleiotropy was assessed by the MVMR-Egger intercept test.

Instrument strength and statistical power

Based on the selected SNPs, we investigated the explained variance in all continuous exposures and computed the F-statistics (univariable MR) as well as conditional F-statistics (MVMR) to quantify the instrument strength as an indicator against weak instrument bias. The statistical power per test was calculated as a function of the underlying unknown true OR for each combination of exposure and outcome.[31]

With regard to multiple testing, p values were Bonferroni adjusted on the basis of 8 null hypotheses and a type I error $\alpha = 0.05$. Network analysis was done in Gephi (V.0.10). The remaining analyses were performed in R (V.4.2.2) using mainly the following packages (version number): LDlinkR (V.1.2.2), mr.raps (V.0.2), Mendelian randomisation (V.0.6.0), MR-PRESSO (V.1.0), RadialMR (V.1.0), MVMR (V.0.3), TwoSampleMR (V.0.5.6), data. table (V.1.14.4), dplyr (V.1.0.10) and ggplot2 (V.3.4.0).

RESULTS
Univariable MR

Starting the iterative process with 120–146 potential genetic instruments (online supplemental tables 1 and 2), which explained between 2.3% and 2.8% of the variance in birth weight related to the fetal effect, the F-statistics representing the instrument strength indicated absence of weak instruments (F≥29.85) (table 2). The number of SNPs used in the analyses regarding the maternal effect ranged from 64 to 74 and had similar F-statistics but explained less variance (1.6 %–1.9 %). Thus, the statistical power was larger in the analyses using the fetal effect phenotype requiring at least true ORs less than 0.63 or larger than 1.37 (arthropathic psoriasis) for a power ≥0.8 (online supplemental figure 1). Statistical

Table 2 Description of instruments depending on exposure and outcome used in the iterative univariable Mendelian randomisation analyses

Characteristic	Rheumatoid arthritis	Multiple sclerosis	Psoriasis	Psoriasis arthritis
Birth weight (fetal effect)				
SNPs used in first iteration	126	120	146	146
SNPs used in last iteration	112	107	142	140
Explained variance by instruments considered*	2.3%	2.3%	2.8%	2.8%
F-statistics, mean (min; max)*	54.48 (29.85; 370.54)	56.35 (29.85; 370.54)	56.93 (29.87; 370.54)	56.93 (29.87; 370.54)
Birth weight (maternal effect)				
SNPs used in first iteration	64	69	74	74
SNPs used in last iteration	57	61	70	72
Explained variance by instruments*	1.6 %	1.8 %	1.9 %	1.9 %
F-statistics, mean (min; max)	51.86 (29.83; 169.74)	52.36 (29.83; 163.92)	53.44 (29.83; 169.74)	53.44 (29.83; 169.74)

*Regarding the first iteration.
SNP, single-nucleotide polymorphism.
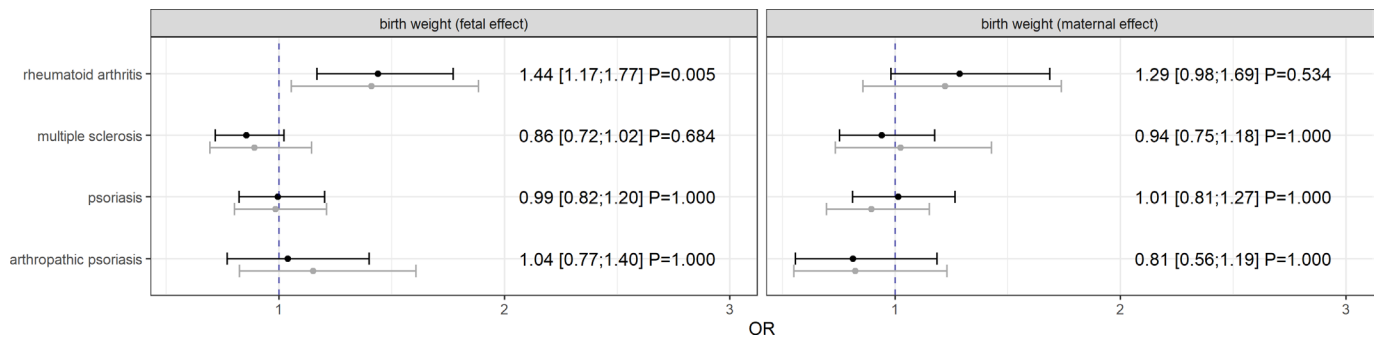
Figure 2 Causal estimates given as ORs and 95% CIs of both fetal and maternal total effects of birth weight on four autoimmune diseases. The grey and the black colours represent the estimates before and after outlier removal, respectively. Presented p values are Bonferroni adjusted.

power was highest for multiple sclerosis and rheumatoid arthritis.

In the following, causal estimates obtained from the radial IVW approach with modified second-order weights were reported as ORs and 95% CIs per SD for the lifetime association of birth weight with a specific autoimmune disease.

Genetically predicted fetal effect birth weight was positively associated with rheumatoid arthritis (OR 1.44; 95% CI 1.17 to 1.77; P_{adj}=0.005) (figure 2). The statistical power for the point estimate and the lower CI was approximately 1 and 0.74, respectively. Remarkably, except CAUSE, all pleiotropy robust approaches led to statistically significant results during all iteration steps and thus confirmed the main result independent of the considered heterogeneity pattern (online supplemental figure 2). From the maternal effect point of view, the association was weaker (OR 1.29; 95% CI 0.98 to 1.69; P_{adj}=0.534) (figure 2). A relationship between birth weight and the remaining autoimmune diseases could not be detected.

Since, despite outlier removal and consistent estimates from the pleiotropy robust methods, there remained some heterogeneity quantified by MR-PRESSO global test (RSS$_{obs}$=147.8; P_{RSS} = 0.014) (online supplemental table 3), we investigated whether there were potential phenotypes responsible for the horizontal pleiotropy. Searching the PhenoScanner database with subsequent network analysis resulted in 14 clusters (online supplemental table 4 and figure 3). Exclusion of the cluster-specific SNPs revealed that the metabolism and obesity related clusters (two largest clusters) may mediate the effect of birth weight on rheumatoid arthritis (figure 3).

Time-varying mediation analysis using MVMR
Considering correlated instruments due to sample overlap, the conditional F-statistics in the multivariable analysis were 11.6, 7.8 and 2.7 for birth weight, adult BMI and childhood BMI, respectively (online supplemental table 5).

Using the robust IVW approach with multiplicative random effects as the principal analysis, the time-varying mediation analysis revealed that the association between birth weight and rheumatoid arthritis was mediated by adulthood BMI only, but not childhood BMI (figure 4). The direct effect after simultaneous adjustment for BMI at both time periods was OR 1.19 (95% CI 0.88 to 1.62; P_{adj}=1) and also confirmed the results after adjustment for BMI of the respective time period (online supplemental figure 4).

As in the univariable analysis no directional pleiotropy (MVMR-Egger intercept=0.002; p=0.379) but substantial heterogeneity was detected (Q=828.43; p=1×10^{-21}) (online supplemental table 5). However, exclusion of 57 outliers of overall 477 SNPs using the MVMR-Lasso method led to even stronger estimates (online supplemental figure 5). In addition, the remaining approaches supported the results from the robust IVW regression.

In summary, the positive association between genetically predicted fetal effect birth weight and rheumatoid arthritis was entirely mediated by BMI in adulthood, as there is no evidence of a direct effect of birth weight on rheumatoid arthritis.

DISCUSSION
In this study, we investigated the cause-and-effect chain between time-varying weight-related body size and the incidence of selected autoimmune diseases. We were able to demonstrate three points in particular. (1) We showed that birth weight increases the risk for rheumatoid arthritis. (2) This risk can be attributed to the fetal rather than the maternal component and (3) is fully mediated by the BMI in adulthood. No causal relationships between birth weight and psoriasis, psoriatic arthritis and multiple sclerosis were found.

Only a small number of previous observational studies investigated the association between birth weight and rheumatoid arthritis.[20 32–35] In a large cohort study including 87 077 women from the Nurses' Health Study, a birth weight >4.54 kg was associated with an increased risk of rheumatoid arthritis in adulthood even after adjustment for potential confounders (relative risk 2.0; 95% CI 1.3 to 3.0).[20] A nationwide register-based case–control study from Sweden found that low birth weight was related to a lower risk of rheumatoid arthritis in individuals aged 16 years and older.[32] Furthermore, a
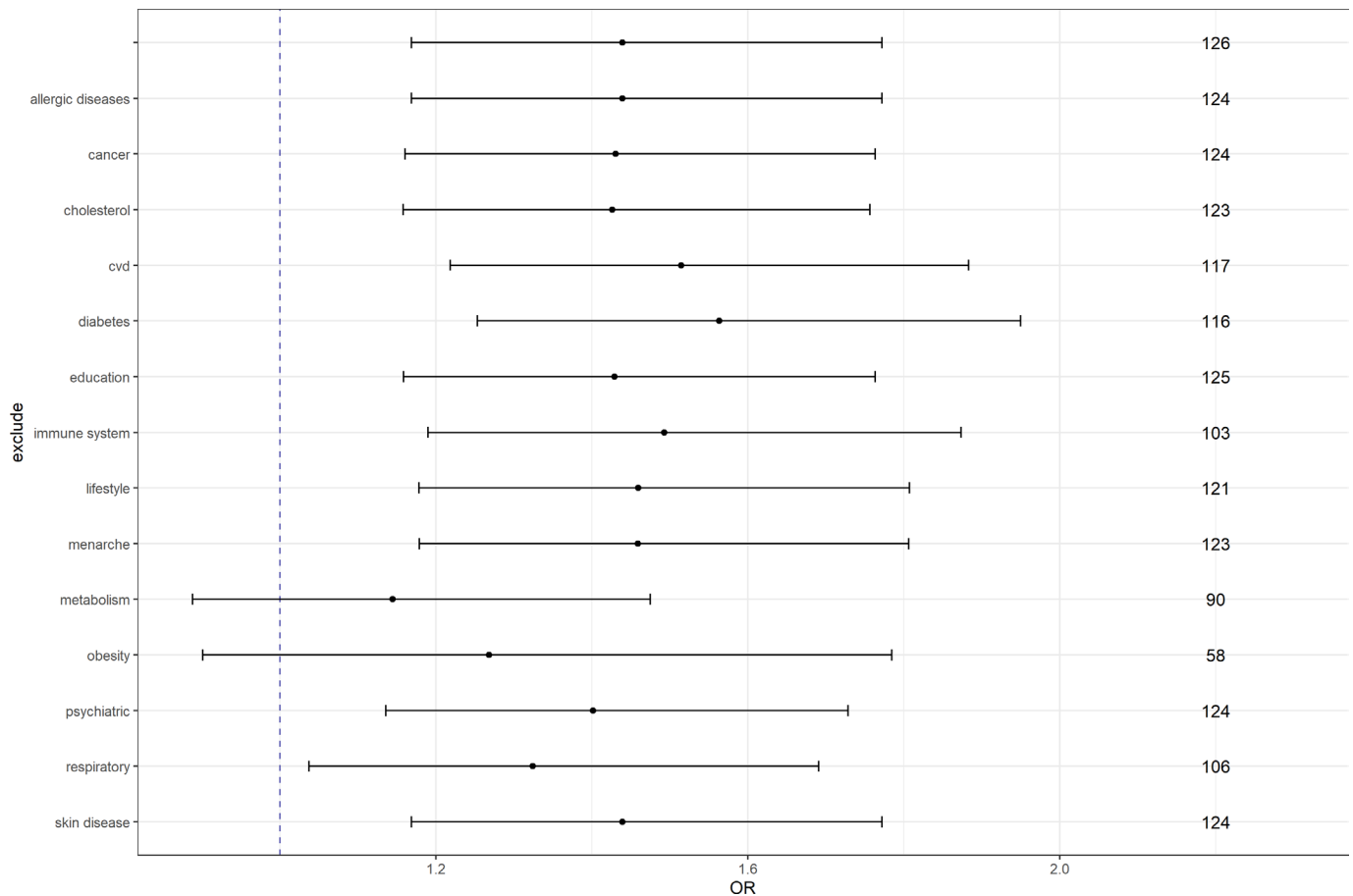
Figure 3 ORs and 95% CIs from MR sensitivity analyses representing the effect of birth weight on rheumatoid arthritis. The main estimate at the top is compared with analyses in which cluster-specific SNPs were omitted. The numbers on the right specify the number of genetic variants after SNP exclusion. SNP, single-nucleotide polymorphism.

national US cohort study including 50 884 women aged 35–74 years reported a significant association between high birth weight (>4000 g) and an increased risk of rheumatoid arthritis after the age of 16 years (OR 1.5, 95% CI 1.1 to 2.1).[33] Results consistent with this were reported by another Swedish study.[34] Contrary, a study on rheumatoid discordant twin pairs could not show an association between birth weight and the manifestation of rheumatoid arthritis in adulthood.[35] The present MR analysis thus extends previous research by suggesting an indirect causal relationship between birth weight and onset of rheumatoid arthritis later in life.

No associations between birth weight and multiple sclerosis was found in this study. The results of previous studies on this topic are partly contradictory. While an observational population-based case–control study from Argentina found an increased risk for multiple sclerosis in individuals with a birth weight of ≥4000 g,[36] another case–control study[37] and a large cohort study[38] showed no associations. A systematic review and meta-analysis confirmed that birth weight does not affect future multiple sclerosis risk[21] and in an MR study on a variety of risk factors for multiple sclerosis no causal relationship was found with birth weight.[39]
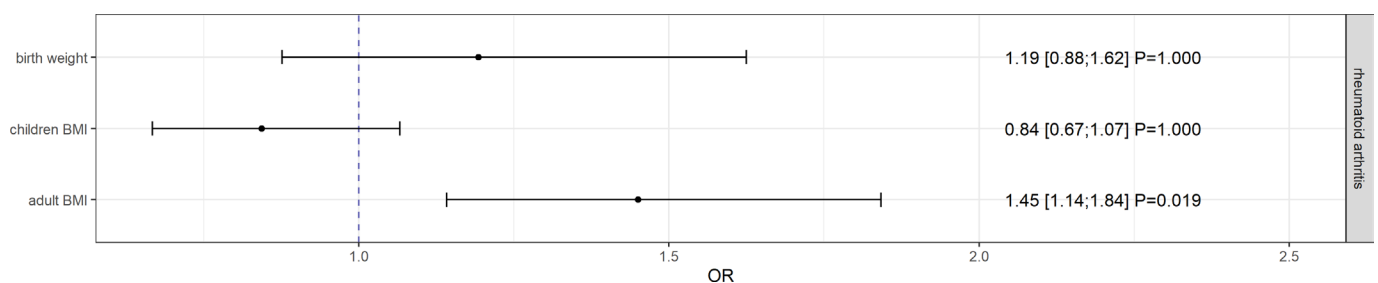
Figure 4 Causal estimates given as ORs and 95% CIs from multivariable MR analysis. The estimate of birth weight on rheumatoid arthritis attenuated when the time-varying mediation-effects of BMI measured in childhood and adulthood were considered. Presented p values are Bonferroni adjusted. BMI, body mass index; MR, Mendelian randomisation.

Furthermore, there was no association between birth weight and psoriasis or psoriatic arthritis in our study. Psoriasis is a complex and multifactorial disease with a genetic basis.[40] An increased susceptibility to disease occurs especially in genetically predisposed populations.[41] In this context, birth weight as an early childhood factor seems to play a rather minor role. As far as we know there are no studies on this topic, why no comparisons can be made with the literature.

Birth weight is a crude indicator of the intrauterine environment, which can be positively or negatively influenced by numerous maternal characteristics.[42] In addition to known risk factors such as smoking and diet, maternal stress experiences before or during pregnancy have been hypothesised to influence fetal growth.[43 44] In rheumatic diseases, dysfunction of the neuroendocrine system is considered one of the risk factors for the development of the diseases in susceptible individuals.[45] It has been discussed that in patients with rheumatoid arthritis, a dysregulation of the hypothalamic–pituitary–adrenocortical (HPA) axis, which produces the key hormone cortisol, are involved in the pathogenesis of the disease.[45 46] Physiological and psychological stressors cause large short-term fluctuations in cortisol levels in pregnant women[47 48] and may be associated with adverse effects on fetal development, such as low birth weight.[49 50] However, previous prenatal studies have reached different conclusions.[51–54] In an observational study, fasting plasma cortisol levels were found to be inversely related to birth weight in men aged 64 years[55] regardless of BMI. Similarly, patients with rheumatoid arthritis have abnormally low cortisol levels,[56] and they are unable to increase cortisol production in the face of chronic inflammation or stress.[57 58] Our results indirectly fit these associations between high birth weight and HPA dysregulation in rheumatoid arthritis.

It has also been hypothesised that there are relationships between neonatal characteristics, including birth weight and future risk for multiple sclerosis.[21] In addition, prenatal stress or exposure to excess glucocorticoids with subsequent hyperreactivity of the HPA axis has been discussed as a feature of multiple sclerosis.[59] This study is consistent with most of the prior observational studies,[38 60 61] systematic reviews and meta-analyses,[21] and an MR study[39] showing no association between birth weight and risk of multiple sclerosis, suggesting that susceptibility to multiple sclerosis is more likely due to other environmental factors in combination with genetic factors.

In this well-powered study, we investigated not only whether birth weight has a causal effect on selected autoimmune diseases, but also whether an association was attributable to the fetal or the maternal component. The iterative MR framework with focus on heterogeneous SNPs and a range of pleiotropy robust sensitivity analyses extended by a conservative network-clustering were used to confirm our results. In addition, by performing a time-varying mediation analysis, we assessed the mediation effect of body composition, which was allowed to vary over a long period of life (from childhood to adulthood).

Our study has certain limitations. MR assumes that the relationship between exposure and outcome is linear, so residual bias may occur when nonlinear relationships, often found in BMI, are modelled. Sample overlap between birth weight and BMI consisting of UK Biobank participants may introduce additional bias. Since all used datasets were restricted to individuals from European descent, the results cannot be generalised to other ethnicities.

In conclusion, a relationship between birth weight and the occurrence of an autoimmune disease later in life most likely does not apply to all autoimmune diseases. Increased birth weight seems to be a risk factor for the future manifestation of rheumatoid arthritis that can be attributed to individuals remaining high BMI into adulthood. Approaches to prevent and minimise the risk could include preventing obesity in adults with high birth weight.

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