Author(s): Pehkonen, Jaakko; Viinikainen, Jutta; Kari, Jaana T.; Böckerman, Petri; Lehtimäki, Terho; Viikari, Jorma; Raitakari, Olli

Title: Birth weight, adult weight, and cardiovascular biomarkers : Evidence from the Cardiovascular Young Finns Study

Year: 2022

Version: Published version

Please cite the original version:

Pehkonen, J., Viinikainen, J., Kari, J. T., Böckerman, P., Lehtimäki, T., Viikari, J., & Raitakari, O. (2022). Birth weight, adult weight, and cardiovascular biomarkers : Evidence from the Cardiovascular Young Finns Study. Preventive Medicine, 154, Article 106894. https://doi.org/10.1016/j.ypmed.2021.106894

Preventive Medicine 154 (2022) 106894

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Birth weight, adult weight, and cardiovascular biomarkers: Evidence from the Cardiovascular Young Finns Study

Jaakko Pehkonen [a,*], Jutta Viinikainen [a], Jaana T. Kari [a], Petri Böckerman [a,b], Terho Lehtimäki [c], Jorma Viikari [d], Olli Raitakari [e]

[a] School of Business and Economics, University of Jyväskylä, Jyväskylä, Finland
[b] Labour Institute for Economic Research, Helsinki, Finland; IZA, Bonn, Germany
[c] Department of Clinincal Chemistry, Tampere University, Finland; Fimlab Laboratoriot Oy Ltd, Tampere, Finland; Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; Finnish Cardiovascular Research Center Tampere, Tampere University, Tampere, Finland
[d] Department of Medicine, University of Turku, Turku, Finland, Division of Medicine, Turku University Hospital, Turku, Finland
[e] Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland; Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland; Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland.

ARTICLE INFO

Keywords:
Causal mediation
Multivariable Mendelian randomization
Birth weight
Adult BMI
Triglycerides
LDL cholesterol

ABSTRACT

This study quantifies the causal effect of birth weight on cardiovascular biomarkers in adulthood using the Cardiovascular Risk in Young Finns Study (YFS). We apply a multivariable Mendelian randomization (MVMR) method that provides a novel approach to improve inference in causal analysis based on a mediation framework. The results show that birth weight is linked to triglyceride levels ($\beta = -0.294$; 95% CI [−0.591, 0.003]) but not to low-density lipoprotein (LDL) cholesterol levels ($\beta = 0.007$; 95% CI [−0.168, 0.183]). The total effect of birth weight on triglyceride levels is partly offset by a mediation pathway linking birth weight to adult BMI ($\beta = 0.111$; 95% CI [−0.013, 0.234]). The negative total effect is consistent with the fetal programming hypothesis. The positive indirect effect via adult BMI highlights the persistence of body weight throughout a person's life and the adverse effects of high BMI on health. The results are consistent with previous findings that both low birth weight and weight gain increase health risks in adulthood.

1. Introduction

Prospective population studies on body weight and health have established two facts. First, overweight and obesity are linked to severe health risks.(Mendis et al., 2011; Reilly and Kelly, 2011; Twig et al., 2016) The evidence based on observational data has gained support from state-of-the-art causal analyses confirming the effect of high body mass index (BMI) on cardiovascular biomarkers such as low-density lipoprotein (LDL) cholesterol and triglycerides.(Bell et al., 2018; Hägg et al., 2015; Holmes et al., 2014) Second, the evidence links birth weight to body mass in childhood (Dubois et al., 2012; Geserick et al., 2018; Hayes et al., 2021) and shows that overweight and obese children are at an elevated risk for becoming overweight adults.(Buscot et al., 2018; Singh et al., 2008) Despite this, research that directly links birth weight to cardiovascular biomarkers in adulthood through adult weight is limited and non-conclusive.(Yu et al., 2011; Risnes et al., 2011)

Identifying the impact of a birth-to-adulthood weight trajectory, or mediating pathways in general, on later-life health outcomes is not straightforward. The difficulties stem from two challenges. First, the effect of birth weight on health may be challenging to identify *a priori*. For example, the fetal programming hypothesis states that undernutrition in the womb during pregnancy causes improper fetal growth. (Barker, 1995) Thus, low birth weight may be a risk for postnatal diseases, and a child with a higher birth weight, owing to modifications in organs during intrauterine life, may be better adapted to risks of nutritional abundance in adulthood.(Hales and Barker, 2013; Kwon and Kim, 2017) On the other hand, traits inherited at birth are likely to be associated with traits later in life; that is, there is a persistence of characteristics over the lifespan.(Alves et al., 2019) Consequently, a higher birth weight is related to a higher adult weight and, therefore, to elevated health risks. Second, identifying causal pathways requires exogenous variation in both the exposure and mediator. However, randomized controlled trials, in which participants are given an intervention that modifies both the exposure and potential mediators, are

* Corresponding author at: Jyväskylä University School of Business and Economics, University of Jyväskylä, Finland.
E-mail address: jaakko.k.pehkonen@jyu.fi (J. Pehkonen).

https://doi.org/10.1016/j.ypmed.2021.106894
Received 17 June 2021; Received in revised form 12 October 2021; Accepted 14 November 2021
Available online 19 November 2021

financially expensive, ethnically challenging, and virtually impossible to conduct in practice.

Our study contributes to the literature on two frontiers. First, examination of the causal effect of birth weight on later-life cardiovascular biomarkers through adult BMI combines two hypotheses—fetal programming and BMI trajectory—into the same model. Second, we use a novel method—multivariable Mendelian randomization (MVMR)—that is based on genetic instruments for both the exposure and mediator in identifying causal pathways.(Carter et al., 2021; Sanderson et al., 2019; Zheng et al., 2017) We are not aware of any prior studies that jointly examine these hypotheses in a causal setting.

Our empirical analysis uses a genotyped longitudinal survey from Finland (the Cardiovascular Risk in Young Finns Study (YFS)) linked to the administrative registers of Statistics Finland. Two well-established cardiovascular biomarkers—triglycerides and LDL cholesterol—are examined.(Mendis et al., 2011; Juonala et al., 2011)

2. Methods

2.1. Study sample

The YFS is a population-based prospective cohort that commenced in 1980 and consists of randomly chosen children ($N = 3596$) from five university hospital districts and their rural surroundings in six age cohorts (aged 3, 6, 9, 12, 15, and 18 years in 1980). Although the YFS is not nationally representative of Finland's total population, it is representative of the six selected age cohorts in the selected geographical areas. (Raitakari et al., 2008; Raitakari et al., 2003)

In 2009, 2442 YFS participants (1123 males and 1319 females) were genotyped. The genotypes were obtained using the Illumina clustering algorithm.(Teo et al., 2007) Quality control was performed using the Sanger genotyping QC pipeline, and individuals with possible relatedness were removed. Genotype imputation was conducted with the SHAPEIT v1 and IMPUTE 2 software,(Delaneau et al., 2012) and the 1000 Genomes Phase I Integrated Release v3 (March 2012 haplotypes) was used as a reference panel.(Howie et al., 2009; Altshuler et al., 2010)

In 2013, data on YFS participants were linked to longitudinal population census (LPC) data of Statistics Finland (permission TK-53-673-13). In 2019, data on several polygenic scores (PGSs) of 2442 YFS participants were added into the database. Supplementary Appendix A reports the summary statistics (Table 1), comparison of the total linked sample to the genotyped subsample (Table 2), and comparison of the genotyped sample to the study sample (Table 3). Supplementary Fig. 1 presents the flowchart of the study sample. In brief, the study sample ($N = 1239$) is representative of the original YFS sample.

2.2. Variables

2.2.1. Birth weight, adult BMI, and health biomarkers in adulthood

Information on the YFS participants' birth weight (kg) was based on parent-reported measurements over the period 1962–1977. The measurement is very likely to be accurate because all parents of a new-born child receive a complete birth certificate at the maternity hospital and a child health clinic card at the child health center containing a measure for birth in kilograms. Adult BMI (weight (kg)/height squared (m^2)) was measured in 2001 by healthcare professionals, which eliminates self-reporting bias. As blood-based biomarkers of health, we used triglyceride and LDL cholesterol levels obtained in 2011 when the YFS participants were between 34 and 49 years of age.

2.2.2. Genetic instruments

The PGSs used as instruments are calculated as a weighted sum of several genetic variants (single nucleotide polymorphisms (SNPs)) that are related to the phenotype (for polygenic score calculation, see Võsa et al. (2021)). The PGS for birth weight (PGS_{BW}) is based on the genome-wide association study (GWAS) of Horikoshi et al.,(Horikoshi et al., 2016) and the PGS for BMI (PGS_{BMI}) is based on the GWAS of Locke et al. (Locke et al., 2015) To maximize the strength of the instruments, we utilize PGSs obtained using a lenient significance threshold ($p < 0.01$). As additional covariates, we use a PGS for waist-to-hip ratio (PGS_{WHR}) based on the GWAS of Shungin et al.(Shungin et al., 2015) and a PGS for triglycerides (PGS_{TRI}) based on the GWAS of Willer et al.(Willer et al., 2013)

2.2.3. Covariates

To account for parental background (socioeconomic status, SES), we use variables from the LPC in 1980. The controls include mother's years of education, father's years of education, an interaction term (mother's years of education × father's years of education), and the logarithm of family income in euros. Using YFS, we also controlled for the region of residence in 1980 via four regional indicators.

2.3. Statistical methods

Fig. 1 depicts the MVMR mediation model. (Carter et al., 2021; Burgess et al., 2015; von Hinke et al., 2016) We used PGSs to estimate the causal links, depicted by solid straight lines. The dashed lines represent the contribution of possible confounders and Mendelian randomization (MR) assumptions. We decompose the total effect of birth weight on a health biomarker into an indirect effect ($\alpha_M\beta_M$) that accounts for the mediated pathway via BMI and a controlled direct effect (β_D).

The MR analysis is based on three key assumptions.(Davies et al., 2018) First, genetic instruments are robustly related to the exposure (*the relevance assumption*). Second, genetic instruments are not associated with any confounders of the exposure–outcome relationship (*the independence assumption*). This assumption could be violated owing to population stratification (the allele frequencies differ between population subgroups), genetic nurturing (the parental genotype indirectly affects offspring's phenotype by influencing parent's phenotype), or assortative mating (the selection of partners based on phenotype).(Brumpton et al., 2020) Third, genetic instruments should affect the outcome only via the exposure (*the exclusion restriction assumption*). This assumption could be violated if genetic instruments affect the outcome via multiple pathways or if they are in linkage disequilibrium (co-inherited) with other genetic variants that affect the outcome via other pathways.(von Hinke et al., 2016; Hemani et al., 2018)

Our research design, based on PGSs instead of individual SNPs, the use of MVMR modeling, and anthropometric measures (birth weight and BMI) obtained by health care professionals mitigates the potential problems of MR in two ways. First, PGSs enhance the strength of the instruments, thus limiting the finite sample bias toward the observational estimate.(Hemani et al., 2018) A strong instrument may also decrease biases stemming from violations of other MR assumptions. (Belsky and Israel, 2014) Second, an anthropometric mediator may be less vulnerable to gene–environmental confounding than educational attainment or health behavior.(McMartin and Conley, 2020; Mills and Tropf, 2020)

Following Sanderson et al.(Sanderson et al., 2019) and Carter et al., (Carter et al., 2021) we examine the causal links in each step of the mediation path. We provide evidence for the link between birth weight and BMI and then between BMI, LDL cholesterol, and triglycerides. The baseline model is augmented with indicator variables for sex, cohort, region of residence in 1980, and parental background. The cohort indicators account for any cohort differences, and regional indicators account for the possibility that genetic variation is clustered by geographical areas. The covariates for family income, parental years of education, and their interactions control for economic resources in childhood and assortative mating.(Brumpton et al., 2020) Next, we apply MVMR to obtain estimates for the indirect and direct effects and report estimates for the total effect. Because the number of observations in our data is limited, the risk of type II error increases. Therefore, we

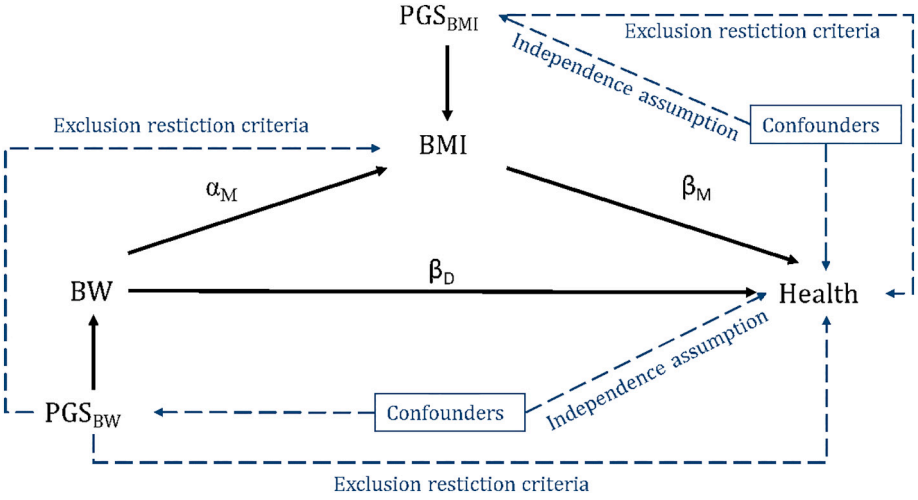

Fig. 1. Mediation of the effect of birth weight (BW) through BMI.
Notes: The indirect effect of BW on the outcome via BMI is obtained by $\alpha_M\beta_M$, and the controlled direct effect is given by β_D.

interpret results with $p < 0.10$ as suggestive evidence for statistical significance. Finally, we conduct robustness analyses.

3. Results

3.1. MR estimates

The MR estimates in Table 1 (panel A, column 1) show that a higher birth weight is related to higher adult BMI ($\beta = 0.111$; $p < 0.05$). The inclusion of the SES and regional controls (column 2) leaves the estimate intact ($\beta = 0.112$; $p < 0.05$). The standard F-statistics (F = 421.93 and F = 409.07) for instrument strength are well above the rule of thumb cut-off of 10 as well as the more conservative cut-off of 100 for genetic instruments proposed by Lee et al.(Staiger and Stock, 1997; Lee et al., 2020)

The MR estimates in panel B (columns 3–6) show that the BMI mediator is causally linked to triglycerides ($\beta = 0.986$; $p < 0.01$) but not to LDL cholesterol ($\beta = 0.173$; $p > 0.10$). As in panel A, the estimates are based on strong instruments (highest F = 204.42; lowest F = 196.22), and the inclusion of the SES and regional controls leaves the estimates intact. In brief, the MR estimates show evidence for the causal link between birth weight and BMI and between BMI and triglycerides but not between BMI and LDL cholesterol.

3.2. MVMR estimates of the direct and indirect effects

The F-statistics in Table 2 show that the instruments strongly predict both the exposure and mediator (F = 204.60 for PGS_{BW} and F = 100.28 for PGS_{BMI}). The Sanderson–Windmeijer (S—W) multivariate F-test further shows that the instruments have sufficient strength to jointly predict the exposure and mediator. The MVMR estimation increased the strength of the instruments (S-W = 374.84 for birth weight and S-W = 191.95 for BMI).

Birth weight is causally associated with the BMI mediator ($\beta = 0.111$; $p < 0.05$ in column 1; $\beta = 0.112$; $p < 0.05$ in column 2), and the BMI mediator is causally associated with triglycerides ($\beta = 0.986$; $p < 0.01$) but not with LDL cholesterol ($\beta = 0.159$; $p > 0.10$). Consequently, we observe a statistically significant indirect effect of birth weight through the mediator for triglycerides ($\beta = 0.111$; $p < 0.10$) but not for LDL cholesterol ($\beta = 0.018$; $p > 0.10$).

The estimates of the total effect ($\beta = -0.294$; $p < 0.10$) and controlled direct effect ($\beta = -0.404$; $p < 0.01$) for triglycerides support the fetal programming hypothesis: a lower birth weight is a health risk. This link is partly offset by mediation via BMI: high birth weight tends to increase adult BMI, and high adult BMI is linked to higher adult triglyceride levels. The absence of the total effect of birth weight on LDL cholesterol ($\beta = 0.007$; $p > 0.10$) and of the controlled direct effect ($\beta = -0.011$; $p > 0.10$) is consistent with the MVMR estimate of no indirect effect via BMI ($\beta = 0.018$; $p > 0.10$).

In brief, birth weight is causally linked to triglycerides but not to LDL

Table 1
MR estimates. The effect of BW on BMI and the effect of BMI on LDL cholesterol and triglycerides.

	Panel A		Panel B			
	The effect of BW on BMI		The effect of BMI on biomarkers			
	BMI		LDL cholesterol		Triglycerides	
	(1)	(2)	(3)	(4)	(5)	(6)
Estimate	0.111**	0.112**	0.173	0.158	0.986***	0.953***
	(0.056)	(0.056)	(0.127)	(0.126)	(0.200)	(0.203)
	[$p = 0.048$]	[$p = 0.047$]	[$p = 0.171$]	[$p = 0.211$]	[$p = 0.000$]	[$p = 0.000$]
First-stage F-statistics	421.93	409.07	204.42	196.22	204.42	196.22
Covariates	Cohort, sex	Cohort, sex SES, region	Cohort, sex	Cohort, sex SES, region	Cohort, sex	Cohort, sex SES, region

Notes: $N = 1239$. The table reports two-stage least squares regression coefficients, standard errors in parenthesis, and p-values in square brackets. Significance at the ***$p < 0.01$, **$p < 0.05$, and *$p < 0.10$ levels. BW and BMI were log transformed. Instruments are PGS_{BW} (panel A) and PGS_{BMI} (panel B). SES consists of log of family income in 1980, mother's years of education in 1980, father's years of education in 1980, and interaction term (mother's years of education × father's years of education). Region refers to the region of residence in 1980 (four indicators).

Table 2
MVMR estimates. The effect of BW on LDL cholesterol and triglycerides via BMI.

	LDL cholesterol	Triglycerides
	(1)	(2)
(1) BW on BMI	0.111**	0.112**
	(0.056)	(0.056)
(2) BMI on biomarker	0.159	0.986***
	(0.127)	(0.206)
(3) Indirect effect via BMI	0.018	0.111*
	(0.019)	(0.062)
	[$p = 0.356$]	[$p = 0.077$]
(4) Controlled direct effect	−0.011	−0.404***
	(0.091)	(0.148)
	[$p = 0.908$]	[$p = 0.006$]
(5) Total effect	0.007	−0.294*
	(0.090)	(0.152)
	[$p = 0.935$]	[$p = 0.053$]
Covariates	Cohort, sex SES, region	Cohort, sex SES, region
F- statistics (BW/BMI)	204.60/100.28	
S–W statistics (BW/BMI)	374.84/191.95	

Notes: N = 1239. See Table 1 for definitions. BW and BMI were log transformed. The total effect is calculated from an MR regression, where the triglyceride level is regressed on BW, which is instrumented with PGS_{BW}. Indirect effects are calculated as a product of coefficients, and their standard errors are based on bootstrapping with 1000 replications.

cholesterol, and there is mediation via adult BMI for triglycerides. The MVMR estimates are consistent with the univariable MR analysis and show that a 10% increase in birth weight leads to a 1.12% higher adult BMI, which translates into an increase of 1.10% in triglycerides.

3.3. Robustness of the MVMR estimates

The MVMR estimates in Table 2 showed evidence that higher birth weight is linked to lower triglyceride levels. Consequently, the robustness analyses in Table 3 focused only on this biomarker. Specification 1 shows the baseline results. Specification 2 augments the model with an indicator for the use of medication designed to lower triglyceride levels. This provides evidence for whether the baseline estimates reflect unaccounted selection in terms of precautionary medical treatment. Specification 3 augments the model with a PGS for triglycerides (PGS_{TRI}) and specification 4 with a PGS for the waist-to-hip ratio (PGS_{HWR}). The former sheds light on possible pleiotropy in the estimates, whereas the latter controls for the possibility that the risks of a high BMI on biomarkers may be modified by the distribution of fat in the body.(Bell et al., 2018; Alves et al., 2019) Specifications 5 and 6 augment the model with indicators for premature infants and low birth weight, respectively. Specification 7 uses inverse probability weights to account for possible non-random attrition bias in the sample study; see Supplementary Appendix B for the construction of the inverse probability weights.

The robustness checks in Table 3 confirm the main findings. In addition, we examined the exclusion restriction by regressing the BMI mediator on the PGS for birth weight, conditioning on birth weight and all baseline covariates, and triglyceride outcome on the PGSs for adult BMI and birth weight, conditioning on BMI, birth weight, and all baseline covariates. The PGSs did not significantly enter into these models ($p = 0.211$ for PGS_{BW} in the first model; $p = 0.276$ for PGS_{BMI} and 0.460 for PGS_{BW} in the second model). Thus, the SNPs included in the instruments for the exposure and mediator seem to be independent; therefore, the change in the controlled direct effect, compared with the total effect, describes causal mediation and is not attributable to pleiotropy.(Carter et al., 2021)

4. Discussion and conclusions

4.1. Key strengths and results

Our research design has two strengths. First, the analyses combined two hypotheses—fetal programming and BMI trajectory—into the same model. Second, we used the MVMR approach for assessing causal pathway and mediation.(Carter et al., 2021; Sanderson et al., 2019; Zheng et al., 2017; Burgess et al., 2015)

We found statistically significant and negative total effect of birth weight on triglycerides. This result is consistent with Barker's hypothesis that low birth weight increases health risks in adulthood.(Zeng and Zhou, 2019) Moreover, the finding that there is no significant total effect of birth weight on LDL cholesterol is consistent with research suggesting that impaired fetal growth does not have effects on cholesterol levels that would have a meaningful impact on the risk of vascular diseases; see Huxley et al.(Huxley et al., 2004) and Knop et al.(Knop et al., 2018) for a meta-analysis. Ramadhani et al.,(Ramadhani et al., 2006) using a sample of young adults in the Netherlands, reported similar results: higher birth weight predicts lower health risk through lower triglycerides,

Table 3
The effect of BW on triglycerides via BMI: robustness analyses.

	MVMR estimates						
	Baseline	Medication added	PGS_{TRI} added	PGS_{WHR} added	Indicator premature infants	Indicator < 2,5 kg BW	Inverse probability weights
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
(1) BW on BMI	0.112**	0.112**	0.110**	0.120**	0.126**	0.126**	0.121**
	(0.056)	(0.056)	(0.056)	(0.054)	(0.063)	(0.061)	(0.055)
(2) BMI on triglycerides	0.986***	0.979***	0.828***	0.747***	1.048***	0.997***	1.003***
	(0.206)	(0.206)	(0.143)	(0.241)	(0.200)	(0.209)	(0.216)
(3) Indirect effect via BMI	0.111*	0.110*	0.091*	0.089*	0.132*	0.126*	0.121*
	(0.062)	(0.063)	(0.054)	(0.051)	(0.073)	(0.070)	(0.062)
	[$p = 0.077$]	[$p = 0.063$]	[$p = 0.094$]	[$p = 0.080$]	[$p = 0.075$]	[$p = 0.060$]	[$p = 0.052$]
(4) Controlled direct effect	−0.404***	−0.418***	−0.319**	−0.367**	−0.403**	−0.417**	−0.410***
	(0.148)	(0.147)	(0.143)	(0.148)	(0.152)	(0.163)	(0.152)
(5) Total effect	−0.294*	−0.313**	−0.228	−0.278*	−0.271*	−0.292*	−0.289*
	(0.152)	(0.150)	(0.147)	(0.149)	(0.168)	(0.165)	(0.155)
	[$p = 0.053$]	[$p = 0.037$]	[$p = 0.121$]	[$p = 0.062$]	[$p = 0.107$]	[$p = 0.078$]	[$p = 0.062$]
F-statistics (BW/BMI)	204.60/ 100.28	204.44/ 99.49	203.81/ 102.01	203.61/ 75.64	186.85/ 103.81	247.38/ 99.72	185.80/ 93.19
S–W statistics (BW/BMI)	374.84/ 191.95	376.32/ 191.11	376.66/ 195.89	341.47/ 142.90	354.78/ 199.31	426.07/ 186.50	343.99/ 178.16

Notes: N = 1239 (in column 5, $N = 1210$). See Table 1 for definitions. BW and BMI were log transformed. Covariates consist of cohort, sex, region, and SES. Indirect effects are calculated as the product of coefficients, and their standard errors are based on bootstrapping with 1000 replications. The total effect is calculated using two-stage least squares regression, where the biomarker is regressed on BW, which is instrumented with PGS_{BW}.

whereas there is no association between birth weight and LDL cholesterol. However, contradictory findings also exist. Using the UK Biobank data, Zanetti et al.(Zanetti et al., 2018) found that birth weight is inversely related to later-life LDL cholesterol but not to triglycerides.

Higher birth weight was linked to higher triglyceride levels via high BMI. This result on the tracking of body weight over an individual's lifespan is consistent with evidence based on observational data,(Bell et al., 2018; Hayes et al., 2021) genotyped data,(Khera et al., 2019; Gill et al., 2021) and YFS data.(Smith et al., 2020) Our estimates show that a 10% increase in birth weight leads to a 1.12% higher adult BMI, which translates into a 1.10% increase in triglycerides. A 10% increase in birth weight, holding adult BMI constant, leads to a 4.0% decrease in triglycerides. Thus, part of the negative total effect of birth weight on triglycerides is offset by an opposing indirect effect via BMI, reflecting the adverse effects of high BMI on health. Although our results support both the fetal programming and BMI trajectory hypotheses, the former mechanism seems to dominate, as the total effect of birth weight on triglycerides is negative. However, the overall importance of weight gain over the lifespan on triglycerides is noteworthy: a 10% increase in adult BMI leads to a 9.8% higher triglyceride level.

4.2. Possible limitations

This study has five possible concerns. First is the possibility of recall errors in the birth weight measure, although parents receive a birth weight certificate at the maternity hospital and birth weight is recorded in the child health clinic card. Second, the identification strategy was based on genetic variation. Variations owing to other factors may have different implications. Third, the analyses assumed that the instruments are valid. The PGSs were based on a lenient significance threshold ($p < 0.01$), which increases the risk of pleiotropy. It is not possible to prove instrument validity, although the use of strong instruments decreases biases stemming from violations of other MR assumptions and the robustness checks were consistent with instrument validity. Fourth, the analyses were based on a sample of unrelated individuals; recent research suggests that MR may be most effectively applied within the family unit.(Brumpton et al., 2020) However, this limitation applies to almost all MR studies, and, for example, a recent study by Cawley et al. (Cawley et al., 2019) on peer effects in BMI showed no evidence of genetic nurture within families. Finally, it is possible that the importance of the indirect effect relative to the direct effect has increased owing to lifestyle changes over time, reflecting possible gene–environment interactions.(Qi and Cho, 2008) Owing to the relatively small study sample, we were unable to test this hypothesis, but further studies could shed light on Barker's hypothesis in this regard.

Funding

The YFS has been financially supported by the Academy of Finland (grant numbers 322098, 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), 41071 (Skidi)); Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio; Tampere and Turku University Hospitals (grant number X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research; Finnish Cultural Foundation; the Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; Jenny and Antti Wihuri Foundation; Diabetes Research Foundation of Finnish Diabetes Association; EU Horizon 2020 (grant number 755320 for TAXINOMISIS); European Research Council (grant number 742927 for MULTIEPIGEN project); Tampere University Hospital Supporting Foundation; the Society of Finnish Clinical Chemistry.

Ethics approval, consent to participate, and consent for publication

All participants of the Young Finns Study provided written informed consent, and the study was approved by local institutional review boards (ethics committees of the participating universities). Parents or guardians provided written informed consent on behalf of the under aged children enrolled in the study. The study does not disclose information concerning individual persons. The linked data have been approved for research purposes by Statistics Finland (SF), under the ethical guidelines of the institution which comply with the national standards.

Availability of data

Other researchers can independently obtain access to the data for replication purposes by the permission from Statistics Finland. To obtain access to the data, please contact Statistics Finland, FI-00022, Helsinki, Finland. The specific instructions to obtain access to the data are available at https://tilastokeskus.fi/tup/mikroaineistot/hakumenettely_en.html

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2021.106894.

References

Altshuler, D.L., Durbin, R.M., Abecasis, G.R., et al., 2010. A map of human genome variation from population-scale sequencing. Nature. 467 (7319), 1061–1073. https://doi.org/10.1038/nature09534.

Alves, A.C., De Silva, N.M.G., Karhunen, V., et al., 2019. GWAS on longitudinal growth traits reveals different genetic factors influencing infant, child, and adult BMI. Sci. Adv. 5 (9), 1–18. https://doi.org/10.1126/sciadv.aaw3095.

Barker, D.J., 1995. Fetal origins of coronary heart disease. BMJ 311 (6998), 171–174. https://doi.org/10.1136/bmj.311.6998.171.

Bell, J.A., Carslake, D., O'Keeffe, L.M., et al., 2018. Associations of body mass and fat indexes with cardiometabolic traits. J. Am. Coll. Cardiol. 72 (24), 3142–3154. https://doi.org/10.1016/j.jacc.2018.09.066.

Belsky, D.W., Israel, S., 2014. Integrating genetics and social science: genetic risk scores. Biodemogr. Soc. Biol. 60 (2), 137–155. https://doi.org/10.1080/19485565.2014.946591.

Brumpton, B., Sanderson, E., Heilbron, K., et al., 2020. Avoiding dynastic, assortative mating, and population stratification biases in Mendelian randomization through within-family analyses. Nat. Commun. 11 (1), 1–13. https://doi.org/10.1038/s41467-020-17117-4.

Burgess, S., Daniel, R.M., Butterworth, A.S., Thompson, S.G., 2015. Network Mendelian randomization: using genetic variants as instrumental variables to investigate mediation in causal pathways. Int. J. Epidemiol. 44 (2), 484–495. https://doi.org/10.1093/ije/dyu179.

Buscot, M.J., Thomson, R.J., Juonala, M., et al., 2018. BMI trajectories associated with resolution of elevated youth BMI and incident adult obesity. Pediatrics. 141 (1) https://doi.org/10.1542/peds.2017-2003.

Carter, A.R., Sanderson, E., Hammerton, G., et al., 2021. Mendelian randomisation for mediation analysis: current methods and challenges for implementation. Eur. J. Epidemiol. https://doi.org/10.1007/s10654-021-00757-1 (0123456789).

Cawley, J., Han, E., Kim, J., Norton, E.C., 2019. Testing for family influences on obesity: the role of genetic nurture. Health Econ. 28 (7), 937–952. https://doi.org/10.1002/hec.3889.

Davies, N.M., Holmes, M.V., Davey, Smith G., 2018. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ. 362 https://doi.org/10.1136/bmj.k601.

Delaneau, O., Marchini, J., Zagury, J.F., 2012. A linear complexity phasing method for thousands of genomes. Nat. Methods 9 (2), 179–181. https://doi.org/10.1038/nmeth.1785.

Dubois, L., Ohm Kyvik, K., Girard, M., et al., 2012. Genetic and environmental contributions to weight, height, and bmi from birth to 19 years of age: an international study of over 12,000 twin pairs. PLoS One 7 (2), e30153. https://doi.org/10.1371/journal.pone.0030153.

Geserick, M., Vogel, M., Gausche, R., et al., 2018. Acceleration of BMI in early childhood and risk of sustained obesity. N. Engl. J. Med. 379 (14), 1303–1312. https://doi.org/10.1056/nejmoa1803527.

Gill, D., Zuber, V., Dawson, J., et al., 2021. Risk factors mediating the effect of body mass index and waist-to-hip ratio on cardiovascular outcomes: Mendelian randomization analysis. Int. J. Obes. https://doi.org/10.1038/s41366-021-00807-4. Published online.

Hägg, S., Fall, T., Ploner, A., et al., 2015. Adiposity as a cause of cardiovascular disease: a Mendelian randomization study. Int. J. Epidemiol. 44 (2), 578–586. https://doi.org/10.1093/ije/dyv094.

Hales, C.N., Barker, D.J.P., 2013. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Int. J. Epidemiol. 42 (5), 1215–1222. https://doi.org/10.1093/ije/dyt133.

Hayes, A.J., Carrello, J.P., Kelly, P.J., Killedar, A., Baur, L.A., 2021. Looking backwards and forwards: tracking and persistence of weight status between early childhood and adolescence. Int. J. Obes. 45 (4), 870–878. https://doi.org/10.1038/s41366-021-00751-3.

Hemani, G., Bowden, J., Davey, Smith G., 2018. Evaluating the potential role of pleiotropy in Mendelian randomization studies. Hum. Mol. Genet. 27 (R2), R195–R208. https://doi.org/10.1093/hmg/ddy163.

von Hinke, S., Davey Smith, G., Lawlor, D.A., Propper, C., Windmeijer, F., 2016. Genetic markers as instrumental variables. J. Health Econ. 45, 131–148. https://doi.org/10.1016/j.jhealeco.2015.10.007.

Holmes, M.V., Lange, L.A., Palmer, T., et al., 2014. Causal effects of body mass index on cardiometabolic traits and events: a Mendelian randomization analysis. Am. J. Hum. Genet. 94 (2), 198–208. https://doi.org/10.1016/j.ajhg.2013.12.014.

Horikoshi, M., Beaumont, R.N., Day, F.R., et al., 2016. Genome-wide associations for birth weight and correlations with adult disease. Nature. 538 (7624), 248–252. https://doi.org/10.1038/nature19806.

Howie, B.N., Donnelly, P., Marchini, J., 2009. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genet. 5 (6), e1000529 https://doi.org/10.1371/journal.pgen.1000529.

Huxley, R., Owen, C.G., Whincup, P.H., Cook, D.G., Colman, S., Collins, R., 2004. Birth weight and subsequent cholesterol levels: exploration of the "fetal origins" hypothesis. JAMA. 292 (22), 2755–2764. https://doi.org/10.1001/jama.292.22.2755.

Juonala, M., Magnussen, Costan G., Berenson, Gerald S., et al., 2011. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N. Engl. J. Med. 20 (365), 1876–1885. https://doi.org/10.1056/NEJMoa1010112.

Khera, A.V., Chaffin, M., Wade, K.H., et al., 2019. Polygenic prediction of weight and obesity trajectories from birth to adulthood. Cell. 177 (3), 587–596. https://doi.org/10.1016/j.cell.2019.03.028.

Knop, M.R., Geng, T.T., Gorny, A.W., et al., 2018. Birth weight and risk of type 2 diabetes mellitus, cardiovascular disease, and hypertension in adults: a meta-analysis of 7 646 267 participants from 135 studies. J. Am. Heart Assoc. 7 (23), e008870 https://doi.org/10.1161/JAHA.118.008870.

Kwon, E.J., Kim, Y.J., 2017. What is fetal programming?: a lifetime health is under the control of in utero health. Obstet. Gynecol. Sci. 60 (6), 506–519. https://doi.org/10.5468/ogs.2017.60.6.506.

Lee, D.S., McCrary, J., Moreira, M.J., Porter, J., 2020. Valid t-ratio Inference for IV. Published online. http://arxiv.org/abs/2010.05058.

Locke, A.E., Kahali, B., Berndt, S.I., et al., 2015. Genetic studies of body mass index yield new insights for obesity biology. Nature. 518 (7538), 197–206. https://doi.org/10.1038/nature14177.

McMartin, A., Conley, D., 2020. Commentary: Mendelian randomization and education-challenges remain. Int. J. Epidemiol. 49 (4), 1193–1206. https://doi.org/10.1093/ije/dyaa160.

Mendis, S., Puska, P., Norrying, B., 2011. Global Atlas on Cardiovascular Disease Prevention and Control.

Mills, M.C., Tropf, F.C., 2020. Sociology, genetics, and the coming of age of sociogenomics. Annu. Rev. Sociol. 46, 553–581. https://doi.org/10.1146/annurev-soc-121919-054756.

Qi, L., Cho, Y.A., 2008. Gene-environment interaction and obesity. Nutr. Rev. 66 (12), 684–694. https://doi.org/10.1111/j.1753-4887.2008.00128.x.

Raitakari, O.T., Juonala, M., Kähönen, M., et al., 2003. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the cardiovascular risk in young Finns study. JAMA. 290 (17), 2277–2283. https://doi.org/10.1001/jama.290.17.2277.

Raitakari, O.T., Juonala, M., Rönnemaa, T., et al., 2008. Cohort profile: the cardiovascular risk in young Finns study. Int. J. Epidemiol. 37 (6), 1220–1226. https://doi.org/10.1093/ije/dym225.

Ramadhani, M.K., Grobbee, D.E., Bots, M.L., et al., 2006. Lower birth weight predicts metabolic syndrome in young adults: the atherosclerosis risk in young adults (ARYA)-study. Atherosclerosis. 184 (1), 21–27. https://doi.org/10.1016/j.atherosclerosis.2005.03.022.

Reilly, J.J., Kelly, J., 2011. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. Int. J. Obes. 35 (7), 891–898. https://doi.org/10.1038/ijo.2010.222.

Risnes, K.R., Vatten, L.J., Baker, J.L., et al., 2011. Birthweight and mortality in adulthood: a systematic review and meta-analysis. Int. J. Epidemiol. 40 (3), 647–661. https://doi.org/10.1093/ije/dyq267.

Sanderson, E., Davey Smith, G., Windmeijer, F., Bowden, J., 2019. An examination of multivariable Mendelian randomization in the single-sample and two-sample summary data settings. Int. J. Epidemiol. 48 (3), 713–727. https://doi.org/10.1093/ije/dyy262.

Shungin, D., Winkler, T., Croteau-Chonka, D.C., et al., 2015. New genetic loci link adipose and insulin biology to body fat distribution. Nature. 518 (7538), 187–196. https://doi.org/10.1038/nature14132.

Singh, A.S., Mulder, C., Twisk, J.W.R., Van Mechelen, W., Chinapaw, M.J.M., 2008. Tracking of childhood overweight into adulthood: a systematic review of the literature. Obes. Rev. 9 (5), 474–488. https://doi.org/10.1111/j.1467-789X.2008.00475.x.

Smith, K.J., Magnussen, C.G., Pahkala, K., et al., 2020. Youth to adult body mass index trajectories as a predictor of metabolically healthy obesity in adulthood. Eur. J. Pub. Health 30 (1), 195–199. https://doi.org/10.1093/eurpub/ckz109.

Staiger, B.Y.D., Stock, J.H., 1997. Instrumental variables regression with weak instruments. Econometrica. 65 (3), 557–586.

Teo, Y.Y., Inouye, M., Small, K.S., et al., 2007. A genotype calling algorithm for the Illumina BeadArray platform. Bioinformatics. 23 (20), 2741–2746. https://doi.org/10.1093/bioinformatics/btm443.

Twig, G., Yaniv, G., Levine, H., et al., 2016. Body-mass index in 2.3 million adolescents and cardiovascular death in adulthood. N. Engl. J. Med. 374 (25), 2430–2440. https://doi.org/10.1056/nejmoa1503840.

Võsa, U., et al., 2021. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. Nat. Genet. 53 (9), 1300–1310. https://doi.org/10.1038/s41588-021-00913-z.

Willer, C.J., Schmidt, E.M., Sengupta, S., et al., 2013. Discovery and refinement of loci associated with lipid levels. Nat. Genet. 45 (11), 1274–1285. https://doi.org/10.1038/ng.2797.

Yu, Z.B., Han, S.P., Zhu, G.Z., et al., 2011. Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. Obes. Rev. 12 (7), 525–542. https://doi.org/10.1111/j.1467-789X.2011.00867.x.

Zanetti, D., Tikkanen, E., Gustafsson, S., Priest, J.R., Burgess, S., Ingelsson, E., 2018. Birthweight, type 2 diabetes mellitus, and cardiovascular disease: addressing the Barker hypothesis with Mendelian randomization. Circ. Genom. Precis. Med. 11 (6), e002054 https://doi.org/10.1161/CIRCGEN.117.002054.

Zeng, P., Zhou, X., 2019. Causal association between birth weight and adult diseases: evidence from a Mendelian randomization analysis. Front. Genet. 10 (JUL), 1–16. https://doi.org/10.3389/fgene.2019.00618.

Zheng, J., Baird, D., Borges, M.-C., et al., 2017. Recent developments in Mendelian randomization studies. Curr. Epidemiol. Rep. 4 (4), 330–345. https://doi.org/10.1007/s40471-017-0128-6.