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Mediating pathways between attention deficit hyperactivity disorder and type 2 diabetes mellitus: evidence from a two-step and multivariable Mendelian randomization study

J. Zhang[1,2], Z. K. Chen[1], R. D. Triatin[1,3], H. Snieder[1], C. H. L. Thio[1,4] and C. A. Hartman[5]

[1]Department of Epidemiology, Unit of Genetic Epidemiology and Bioinformatics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [2]Division of Communicable Disease Control and Prevention, Shenzhen Center for Disease Control and Prevention, Shenzhen, Guangdong, China; [3]Faculty of Medicine, Department of Biomedical Sciences, Universitas Padjadjaran, Bandung, Indonesia; [4]Department of Population Health Sciences, Institute for Risk Assessment Sciences, University of Utrecht, Utrecht, The Netherlands and [5]Interdisciplinary Centre Psychopathology and Emotion Regulation, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

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Corresponding author: C. A. Hartman; Email: c.a.hartman@umcg.nl

Abstract

Aims. Type 2 diabetes (T2D) is a global health burden, more prevalent among individuals with attention deficit hyperactivity disorder (ADHD) compared to the general population. To extend the knowledge base on how ADHD links to T2D, this study aimed to estimate causal effects of ADHD on T2D and to explore mediating pathways.

Methods. We applied a two-step, two-sample Mendelian randomization (MR) design, using single nucleotide polymorphisms to genetically predict ADHD and a range of potential mediators. First, a wide range of univariable MR methods was used to investigate associations between genetically predicted ADHD and T2D, and between ADHD and the purported mediators: body mass index (BMI), childhood obesity, childhood BMI, sedentary behaviour (daily hours of TV watching), blood pressure (systolic blood pressure, diastolic blood pressure), C-reactive protein and educational attainment (EA). A mixture-of-experts method was then applied to select the MR method most likely to return a reliable estimate. We used estimates derived from multivariable MR to estimate indirect effects of ADHD on T2D through mediators.

Results. Genetically predicted ADHD liability associated with 10% higher odds of T2D (OR: 1.10; 95% CI: 1.02, 1.18). From nine purported mediators studied, three showed significant individual mediation effects: EA (39.44% mediation; 95% CI: 29.00%, 49.73%), BMI (44.23% mediation; 95% CI: 34.34%, 52.03%) and TV watching (44.10% mediation; 95% CI: 30.76%, 57.80%). The combination of BMI and EA explained the largest mediating effect (53.31%, 95% CI: −1.99%, 110.38%) of the ADHD–T2D association.

Conclusions. These findings suggest a potentially causal, positive relationship between ADHD liability and T2D, with mediation through higher BMI, more TV watching and lower EA. Intervention on these factors may thus have beneficial effects on T2D risk in individuals with ADHD.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most prevalent childhood psychiatric disorders affecting around 5–7% of children (Faraone *et al.*, 2015; Polanczyk *et al.*, 2014; Thomas *et al.*, 2015). It is characterized by extensive hyperactive, impulsive and inattentive behaviours that impair daily functioning, e.g. at school, work or in social relations (Breslau *et al.*, 2011; Fleming *et al.*, 2017; Ros and Graziano, 2018). In most children, ADHD persists during adolescence and into adulthood, either at full syndromal or subthreshold clinical levels (Faraone *et al.*, 2006). Prevalence estimates of ADHD in adulthood are 2–3% (Simon *et al.*, 2009).

Type 2 diabetes (T2D) is a multifactorial disorder in which impaired insulin secretion and/or insulin resistance results in dysregulated carbohydrate, lipid and protein metabolism (DeFronzo *et al.*, 2015). T2D is typically an adult-onset disease manifesting at middle or older ages (Carstensen *et al.*, 2020; Sun *et al.*, 2022), although more recently a substantial increase among younger people (aged <40 years) is observed, significantly boosting premature morbidity

and mortality (Magliano *et al.*, 2020; Viner *et al.*, 2017). The global prevalence has been continuously rising over the past few decades, with T2D projected to affect 12.2% (783 million) of the world population by the year 2045 (Sun *et al.*, 2022), thus posing an increasingly unsustainable global health burden (Vos *et al.*, 2020).

Epidemiological studies have shown a higher T2D prevalence (up to 70%) among individuals with ADHD compared to the general population (Chen *et al.*, 2018b, 2018a). Meta-analysis estimated a twofold higher risk of T2D in individuals with ADHD (Garcia-Argibay *et al.*, 2023). In addition, recent evidence suggests an earlier onset of T2D in those with ADHD than those without (Chen *et al.*, 2018a). As a childhood onset condition, ADHD manifests much earlier than T2D, suggesting that ADHD, or factors/behaviours related to ADHD, precede and possibly cause T2D. However, it is currently unclear if the association between ADHD and T2D indeed represents a causal link and, if such link exists, how ADHD could lead to the onset of T2D.

Several factors could explain a potential link between ADHD and T2D. First, known precursors of T2D, such as obesity (Cortese *et al.*, 2016; Güngör *et al.*, 2016) and sedentary behaviour (Cook *et al.*, 2015), are also more common in individuals with ADHD compared to those in the general population. It is plausible that the behaviours involved in ADHD such as impulsivity may enhance the chance of overeating or poor diet, leading to obesity (Cortese and Castellanos, 2014) in turn leading to T2D (Landau and Pinhas-Hamiel, 2019). Also, screen time utilization is longer among individuals with ADHD and may partly explain the relation between sedentary behaviours and T2D (Nightingale *et al.*, 2017; Yang *et al.*, 2022). Second, ADHD is strongly linked to lower educational attainment (EA) (Fleming *et al.*, 2017; Korrel *et al.*, 2017), potentially due to early school dropout or poor school performance, although such causal pathways are currently unclear (Hartman, 2020). Evidence from observational studies and genetic studies have suggested that lower EA and T2D are causally linked (Agardh *et al.*, 2011; Zhang *et al.*, 2022). Lower EA may thus be an important pathway connecting ADHD and T2D. Third, individuals with ADHD are at increased risk for cardiovascular diseases (Akmatov *et al.*, 2021; Chen *et al.*, 2018b; Li *et al.*, 2022b, 2023), elevated blood pressure (Chen *et al.*, 2018b) and increased peripheral inflammation (Saccaro *et al.*, 2021). These well-known risk factors of T2D (Emdin *et al.*, 2015; Wang *et al.*, 2012) may also be mediators between ADHD and T2D, although a recent register-based study focused on referred and diagnosed patients (i.e. more severely affected patients) suggests that cardiovascular traits played only a minor mediating role (Garcia-Argibay *et al.*, 2023). Despite the plausibility of these pathways, it is not known whether, and to what extent, these are mechanisms explaining the association of ADHD with T2D. A better understanding of causal mechanisms may help prevention of T2D in individuals with ADHD. Therefore, research on mediating pathways is needed (Byrne *et al.*, 2017; Hartman, 2020).

A widely applied method that supports causal inference from observational data is Mendelian randomization (MR), which uses genetic instrumental variables to examine the relationship between a risk factor (in this case ADHD), and a disease outcome (T2D) (Smith and Ebrahim, 2003). Under a number of assumptions, MR yields a causal estimate, i.e. an estimate that is less likely to be biased due to confounding, the primary source of bias in observational studies (Smith and Ebrahim, 2004). According to Mendel's laws of random segregation and independent assortment, alleles are assigned randomly before conception, independently of other traits. Thus, genetic variants can be exploited as a natural experiment. Recent advances in MR methodology include multivariable MR (MVMR), which among other things can be applied to investigate mediation (Sanderson, 2021).

In recent years, MR has been applied to study effects of ADHD on a wide range of outcomes (*see, for an overview,* Riglin and Stergiakouli, 2022), including but not limited to ischemic stroke (Du *et al.*, 2023), Parkinson's disease (Li *et al.*, 2020), insomnia (Gao *et al.*, 2019), autism spectrum disorder (Baranova *et al.*, 2022), body mass index (BMI) or obesity (Karhunen *et al.*, 2021; Liu *et al.*, 2021; Martins-Silva *et al.*, 2019), substance use (Treur *et al.*, 2021) and socio-economic status (SES) (Michaëlsson *et al.*, 2022). One previous MR study reported a positive relationship between ADHD and T2D (Leppert *et al.*, 2020). Our study aimed to improve on previous studies in two ways. First, we aimed to update ADHD-T2D effect estimates using the most recent genome-wide association studies (GWAS) on ADHD (Demontis *et al.*, 2023) and T2D (Mahajan *et al.*, 2018), which, due to their larger sample sizes, have yielded more precise estimates of genetic effects. Second, we aimed to identify potential mediating pathways that link ADHD to T2D, specifically BMI, sedentary behaviour, EA, smoking, C-reactive protein (CRP), systolic blood pressure (SBP), diastolic blood pressure (DBP).

Methods

Study design

This is an MR study that investigated the relation between ADHD and T2D, and potential mediation through BMI, childhood obesity, childhood BMI, sedentary behaviour (daily hours of TV watching), blood pressure (SBP, DBP), CRP and EA. MR uses genetic instruments to genetically predict an exposure trait. Here, we used single nucleotide polymorphisms (SNPs) as genetic instruments. MR yields causal estimates under three key assumptions: (1) relevance, (2) exchangeability and (3) exclusion restriction (for more details, see **ESM Methods**). We used two-sample MR (2SMR) methods that uses SNP-trait associations available from GWAS summary data (Burgess *et al.*, 2013). We obtained summary statistics of the genetic associations from the most recent GWAS for each respective phenotype (details in Table 1). To determine whether a trait mediates the effect between exposure and outcome, two-step 2SMR was performed (Relton and Davey Smith, 2012). The first step involves genetically predict ADHD and estimating its association with potential mediators. The second step involved genetically predicting these mediators and estimating their effect on the outcome while accounting for ADHD using MVMR. Then, the overall effect of ADHD was separated into an indirect effect (i.e. the effect of ADHD on T2D via the mediator) and a direct effect (i.e. the effect of ADHD on T2D independent of the mediator). The distinct analysis steps for mediation analysis, as well as the decision algorithm on which variables to take forward to the subsequent step, are outlined in Fig. 2. Reporting of the present study was done in accordance with STROBE-MR guidelines (**ESM STROBE-MR**) (Skrivankova *et al.*, 2021a, 2021b).

Variable definitions

The original GWAS defined T2D using a diagnostic fasting glucose, casual glucose level or plasma glucose level of 2 hours or an HbA_{1c} level; use of glucose-lowering medication (by Anatomical Therapeutic Chemical code or self-report); or a history of T2D based on electronic medical records, self-report or a combination of these (Mahajan *et al.*, 2018).

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Table 1. Overview of GWAS data used

Phenotype	Unit	Number of participants	Number of lead SNPs	Explained variance by lead SNPs	Ancestry	Consortium/ cohort	Author	Year of publication	PubMed ID
ADHD	Log-odds	38,691 cases 186,843 control participants	27		European	iPSYCH + deCODE + PGC	Demonis et al.	2023	36702997
Childhood BMI	kg/m^2	61,111	25	3.6%	European	ECG	Vogelezang et al.	2020	33045005
Childhood obesity	Yes vs no	13,005 cases 15,599 control participants	18		European	ECG	Bradfield et al.	2019	31504550
Years of schooling	SD (4.2 years)	1,131,881	1271	11%	European	SSGAC	Lee et al.	2018	30038396
BMI	kg/m^2	681,275	941	6%	European	GIANT	Yengo et al.	2018	30124842
SBP	mmHg	775,601	970	5.7%	European	UKBB + ICBP	Evangelou et al.	2018	30224653
DBP	mmHg	775,601	962	5.3%	European	UKBB + ICBP	Evangelou et al.	2018	30224653
Type 2 diabetes	Yes vs no	74,124 cases 824,006 control participants	403	18%	European	DIAGRAM	Mahajan et al.	2018	30297969
Smoking initiation	Ever vs never	557,337 cases 674,754 control participants	378	2.3%	European	GSCAN	Liu et al.	2019	30643251
CRP	mg/L	204,402	58	7%	European	CIWG	Ligthart et al.	2018	30388399
TV watching	SD (1.5 hours)	408,815	152	2.3%	European	UKBB	van de Vegte et al.	2020	32317632

PGC, Psychiatric Genomics Consortium; DIAGRAM, DIAbetes Genetics Replication And Meta-analysis; EGG, Early Growth Genetics; GIANT, Genetic Investigation of Anthropometric Traits; GSCAN, GWAS & Sequencing Consortium of Alcohol and Nicotine use; ICBP, International Consortium for Blood Pressure; SSGAC, Social Science Genetic Association Consortium; UKBB, UK Biobank; CIWG, Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Inflammation Working Group.

In the original GWAS (Demontis *et al.*, 2023), ADHD cases were diagnosed by psychiatrists at in- or out-patient clinics according to the ICD10 criteria (F90.0, F90.1, F98.8 diagnosis codes) or individuals that have been prescribed medication specific for ADHD symptoms (ATC-NA06BA, mostly methylphenidate).

In selecting mediators, we considered potential for modification, observational epidemiological evidence that link these to both ADHD or T2D, as well as the availability of comprehensive GWAS data. BMI was calculated by dividing weight (kg) by height squared (m^2) (Yengo *et al.*, 2018). Sedentary behaviour was proxied by daily hours of TV watching (in standard deviations, 1.5 hours) (van de Vegte *et al.*, 2020). SBP and DBP were derived from two automated or two manual blood pressure measurements (Evangelou *et al.*, 2018). Smoking was defined as ever-smoking vs never-smoking (Liu *et al.*, 2019). EA was defined as years of schooling (in standard deviations, 4.2 years) based on the International Standard Classification of Education (ISCED) 2011 (Lee *et al.*, 2018; UNESCO Institute for Statistics., 2012). Serum CRP was measured in mg/L using standard laboratory techniques, and was transformed by its natural logarithm in the original GWAS (Ligthart *et al.*, 2018). Childhood obesity was defined as $\geq$95th percentile of BMI achieved 2–18 years old (Bradfield *et al.*, 2019), and childhood BMI was measured in children aged between 2 and 10 years (Vogelezang *et al.*, 2020).

Instrument selection

In Table 1, all identified SNPs, and their associations with T2D, mediators, and ADHD were extracted from summary GWAS data. From the most recent GWAS meta-analysis of ADHD, which included 38,691 people with ADHD and 186,843 controls, 27 SNPs ($p < 5 \times 10^{-8}$) were chosen as genetic instruments for ADHD (Demontis *et al.*, 2023). We applied strict linkage disequilibrium (LD) clumping thresholds for ADHD genetic instruments (LD cut-off of $r^2 < 0.001$ within a window of 10 MB), leading to the removal of 2 out of 27 SNPs. We oriented SNP alleles for ADHD towards positive coefficients, and harmonized the SNP alleles from the outcome GWAS accordingly. We inferred the strand for palindromic SNPs using allele frequencies, and removed ambiguous palindromes (minor allele frequency between 0.42 and 0.58). Figure 1 shows the SNP selection procedure for the ADHD-T2D analysis. It should be noted that the ADHD genetic effect was estimated on the liability scale and not on the yes/no scale. We applied the same criteria to select genetic instruments for each mediator (see Table 1 for details on each GWAS). Detailed information on SNPs and their associations with ADHD, mediators and T2D can be found in **ESM SNP Data**.

Univariable MR analysis

To estimate the univariable associations between genetically predicted ADHD and T2D, and between genetically predicted ADHD and mediators we used a number of methods. First, we performed conventional random-effects inverse variance weighted (IVW) MR of single-SNP Wald ratios (SNP-outcome divided by SNP-exposure association), examining heterogeneity statistics to assess potential pleiotropy, and Egger intercepts to assess potential directional pleiotropy. In addition, we performed a large range of MR sensitivity analyses. In total, we used 44 univariable MR strategies (11 distinct MR estimation methods × Steiger filtering yes/no × outlier filtering yes/no). We applied the MR mixture-of-experts (MR-MoE) machine learning framework to assist in selecting the MR estimate most likely to be reliable (Hemani *et al.*, 2017). MR-MoE prioritizes methods based on certain characteristics of the data such as heterogeneity and directional pleiotropy, and discards instruments that are possibly invalid (e.g. potentially pleiotropic outliers and/or 'reverse causal' SNPs). The top ranked MR estimates for each univariable association were taken forward to further analysis.

MVMR analysis

We estimated the ADHD-adjusted association between each mediator and T2D risk using regression-based MVMR-IVW (Burgess and Thompson, 2015), using trait-specific instruments in addition to ADHD instruments.

Mediation analysis

To calculate the indirect effect of each individual mediator (childhood BMI/obesity, BMI, SBP, DBP, smoking, CRP, EA and TV watching), we used the product-of-coefficients approach. This involved multiplying the ADHD–mediator association (derived from univariable MR) with the ADHD-adjusted association between mediator and outcome (Burgess *et al.*, 2015). The indirect effect was divided by the total effect to assess the proportion of the overall effect of ADHD on T2D that was mediated by each individual mediator. We used the bootstrap method and delta method to estimate the confidence interval for the indirect effect and the proportion mediated.

We investigated indirect effects of multiple mediators combined (e.g. BMI + EA) using the difference in regression coefficient method. This involved subtracting the direct effect of ADHD on T2D (after adjustment for the mediators in MVMR) from the total effect of ADHD on T2D (from univariable MR), to obtain the indirect effect through multiple mediators. To identify the combination with the largest proportion mediated, and to evaluate potential overlapping effects between mediators, we looked into all combinations of mediators.

Mediators were selected into the final analysis if they met the following requirements: (1) ADHD affects the mediator in univariable MR; (2) The mediator affects T2D risk independent of ADHD in an MVMR model (see Fig. 2).

Sensitivity analyses

As an alternative to the product-of-coefficients method to calculate indirect effects through individual mediators, we used the difference in regression coefficient method. The robustness of the MVMR-IVW results was evaluated using the MVMR-Egger method (Rees *et al.*, 2017). We investigated potential bidirectional relationship between ADHD and possible mediators in reverse MR analysis (genetic instruments for each mediator as the exposure).

All MR analyses were conducted using R (version 4.2.1) (Team RC, 2014) and the *TwoSampleMR* R package v0.5.7 (Hemani *et al.*, 2018).

Results

Univariable MR analysis

We included 25 SNPs as genetic instruments for ADHD (Fig. 1). Conventional random-effects IVW estimated a significant positive association between ADHD liability and T2D (OR: 1.15; 95% CI:

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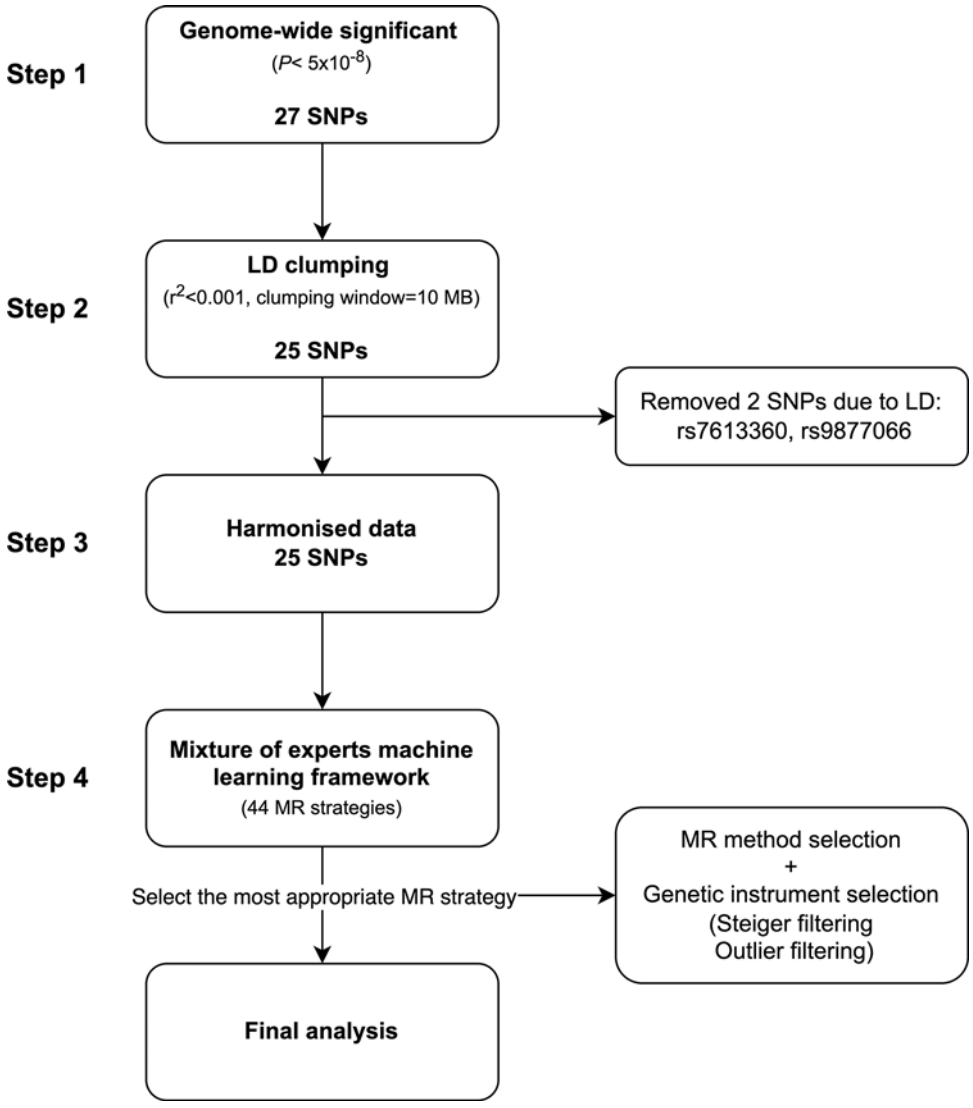

Figure 1. ADHD instrument selection for ADHD-T2D association. LD, linkage disequilibrium; T2D, type 2 diabetes; MR, Mendelian randomization.

1.12, 1.18) in the presence of heterogeneity (Q [df] = 102.2 [24], heterogeneity p-value = 1.26×10^{-11}) but absence of directional pleiotropy (Egger intercept = −1.50 ± 1.59, Egger intercept p-value = 0.357) (**ESM Table S1**). In the results of all 44 univariable MR strategies, associations of ADHD liability with T2D ranged from OR 0.99 (simple mean, no Steiger filtering, no outlier filtering) to OR 1.28 (random effects MR Egger, Steiger filtering, no outlier filtering). Overall, results from the various MR strategies converged to a positive association. MoE assigned the weighted median MR estimate (no Steiger filtering, no outlier filtering) to be the most reliable, which estimated ADHD liability to associate with 10% higher odds of T2D (OR: 1.10; 95% CI: 1.02, 1.18; MoE score: 0.72, **ESM Table S2**).

Associations of genetically predicted ADHD liability with each candidate mediator are shown in Fig. 3a. In the MR models prioritized by MoE (**ESM Table S2**), genetically predicted ADHD liability associated with higher BMI ($\beta = 0.05$ kg/m^2; 95% CI: 0.02, 0.07); more TV watching ($\beta = 0.07$ SD of TV watching; 95% CI: 0.05, 0.08, translating to 0.10 h more TV watching); higher odds of smoking (OR: 1.19; 95% CI: 1.14, 1.24); higher level of circulating CRP ($\beta = 0.06$; 95% CI: 0.02, 0.11), lower EA ($\beta = -0.06$ SD in years of schooling; 95% CI: −0.08, −0.03, translating to 0.25 less years of schooling). Genetically predicted ADHD liability was not associated with childhood obesity or childhood BMI. We observed an inverse association between liability of ADHD and blood pressure (SBP: $\beta = -0.62$; 95% CI: −1.29, 0.04; DBP: $\beta = -0.38$; 95% CI: −0.71, −0.04). Six potential mediators were taken forward to the next step, i.e. MVMR analysis of the ADHD-adjusted effect of mediators (i.e. BMI, TV watching, smoking, CRP, EA and DBP) on T2D (Fig. 2).

MVMR analysis

Figure 3b shows associations of genetically predicted mediators on T2D with adjustment for ADHD using MVMR. A 1 kg/m^2 higher genetically predicted BMI associated with 2.52 times higher odds of T2D (95% CI: 2.14, 2.97). One SD (4.2 years of schooling) higher genetically predicted EA associated with lower odds of T2D (OR: 0.52; 95% CI: 0.45, 0.61). One SD (1.5 hours) of genetically predicted TV watching associated with 1.88 times higher odds of T2D (95% CI: 1.55, 2.28). No associations with T2D were found for genetically predicted smoking (OR: 1.11; 95% CI: 0.98, 1.25),

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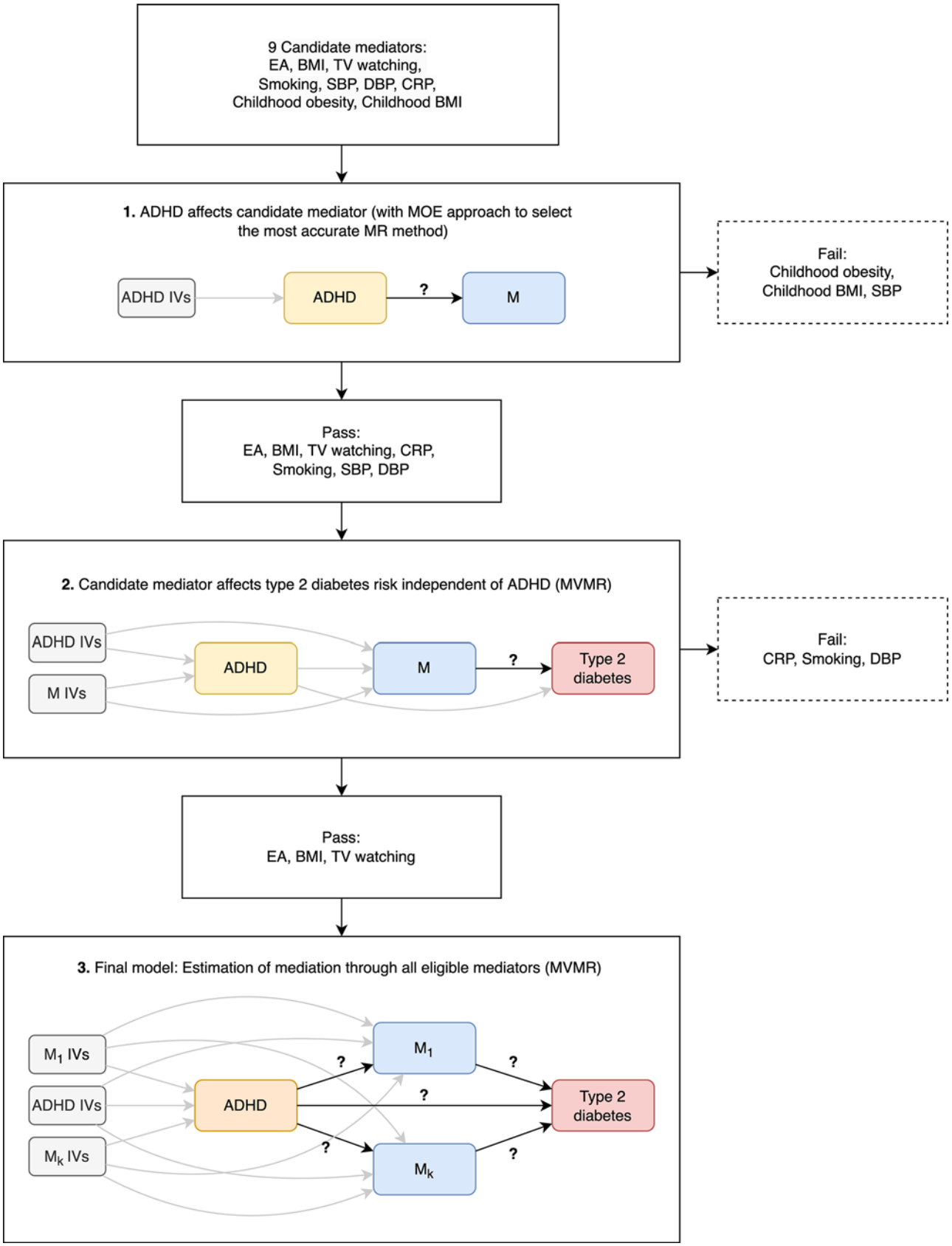

Figure 2. Decision algorithm for mediator selection in the final analysis. MR, Mendelian randomization; MVMR, Multivariable Mendelian randomization; MoE, mixture of experts; ADHD, Attention deficit hyperactivity disorder; EA, educational attainment; BMI, body mass index; TV watching, television watching; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-Reactive Protein; IV, instrument variable.

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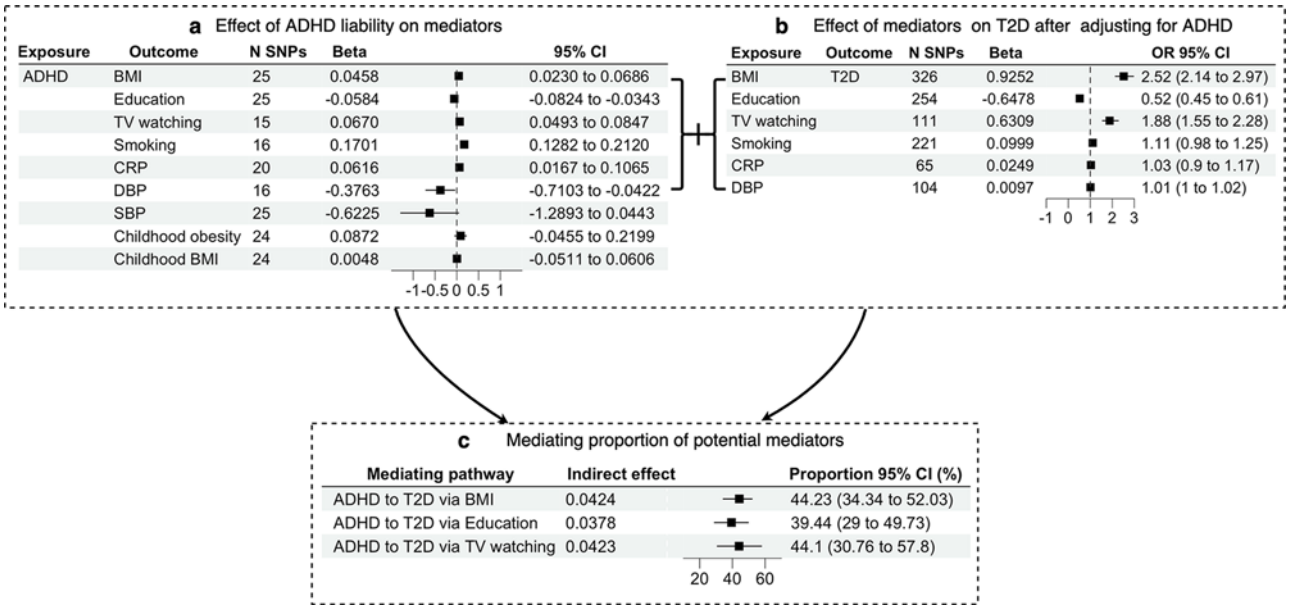

Figure 3. (a) MR-estimated effects of ADHD liability on each mediator separately, presented as Beta with 95% CI. (b) MR-estimated effects of each mediator separately on type 2 diabetes after MVMR adjustment for ADHD, presented as Beta /OR with 95% CI. (c) MR-estimated effects of indirect effects of each mediator separately, by product-of-coefficients method with bootstrap method-estimated 95% CIs. MR-estimated proportions mediated (%) are presented with 95% CIs. OR, odds ratio; CI, confidence interval; ADHD, Attention deficit hyperactivity disorder; BMI, body mass index; TV watching, television watching; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-Reactive Protein; T2D, type 2 diabetes.

CRP (OR: 1.03; 95% CI: 0.90, 1.17) and DBP (OR: 1.01; 95% CI: 0.99, 1.02). Consequently, BMI, EA and TV watching were taken forward to the final mediation analysis.

Mediation analysis

Figure 3c displays the proportion of the effect of ADHD liability on T2D explained by each mediator separately. BMI mediated 44.23% (95% CI: 34.34%, 52.03%) of the total effect of ADHD liability on T2D. EA mediated 39.44% (95% CI: 29.00%, 49.73%) of the total effect, whereas TV watching mediated 44.10% (95% CI: 30.76%, 57.80%).

We examined the proportion mediated of different combinations of BMI, TV watching and EA. This was done in an effort to find the combination that explained the most variance in the ADHD–T2D association, as well as to investigate potential overlap in effects between mediators.

Combining EA with any one of the other mediators resulted in a combined proportion mediation estimate of 40–50% (Table 2). Among the two-mediator combinations, EA + BMI explained the largest combined mediation effect (53.31; 95% CI: −1.99%, 110.38%) of the estimated effect of ADHD liability on T2D. The EA + TV combination showed subtly lower proportion mediated (51.28%; 95% CI: −20.90%, 123.89%). BMI + TV showed less mediating effect (26.87%, 95% CI: −36.96%, 90.89%), suggesting overlapping mediating pathways between higher BMI and TV watching.

The full three-mediator combination (BMI + EA + TV) did not result in a higher estimate of combined proportion mediated (45.99%, 95% CI: −6.80%, 98.73%), again suggesting overlapping effects between these three. For all mediator combinations, delta method estimation of confidence intervals was consistent with the bootstrap method, with wider intervals that all included zero (**ESM Table S3**).

Sensitivity analyses

To assess the consistency of our main MR product-of-coefficients estimates of individual mediation, we performed additional MVMR mediation analysis using the difference in regression coefficient method. Although the estimated indirect effect through BMI was lower, estimates for EA and TV watching were generally similar (**ESM Figure S1**). Results from MVMR-Egger sensitivity analyses showed no significant effects (**ESM Table S4**). However, given the absence of evidence for directional pleiotropy, we consider the MVMR-IVW estimates to be reliable. There was reasonable instrument strength ($F > 10$) of SNPs for EA, BMI and TV in all MVMR analyses. However, conditional instrument strength for ADHD was low.

In reverse MR analyses, higher EA suggestively reduced liability of ADHD (OR: 0.30, 95% CI: 0.26, 0.35), whereas more smoking, hours of TV watching and a higher BMI increased the liability of ADHD (**ESM Table S5, ESM Figure S2**).

Discussion

This study used a two-step MVMR approach to test a putative causal effect of ADHD on T2D, and to explore potential mediators in this relation. ADHD, instrumented by 25 SNPs, was associated with 10% higher odds of T2D (OR: 1.10). Individually, BMI, EA and TV watching mediated 39–44% of the relation, with up to 53% mediation when combining multiple mediators. However, confidence intervals were wide and included zero for each combination. While a simulation study has shown little evidence of bias in MR point estimates of mediation effect, the indirect effect and the proportion mediated estimate may have large error terms in case of a modest total effect (Carter *et al.*, 2021). Therefore, the estimated proportions mediated are likely reliable, but some caution in interpretation is warranted for the error terms.

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Table 2. Estimates of proportion mediated by combinations of factors

			IDE and 95% CI			Prop and 95% CI		
Combinations	Total effect	Direct effect	IDE	LL	UL	Prop	LL	UL
BMI + EA	0.0958	0.0448	0.0511	−0.0019	0.1058	53.31	−1.99	110.38
BMI + TV	0.0958	0.0701	0.0258	−0.0350	0.0871	26.87	−36.96	90.89
EA + TV	0.0958	0.0467	0.0492	−0.0200	0.1188	51.28	−20.90	123.89
BMI + EA + TV	0.0958	0.0518	0.0441	−0.0065	0.0946	45.99	−6.80	98.73

IDE, indirect effect; LL, lower limit; UL, upper limit; CI, confidence interval; Prop, proportion; BMI, body mass index; EA, educational attainment; TV, television.

For the effect magnitude of ADHD on T2D, our study corroborated the estimate of a previous MR study that used 11 ADHD SNPs (OR: 1.09) (Leppert *et al.*, 2020). This estimate is however smaller than the OR reported in a recent study that used 26 instruments (OR: 1.30) (Baranova *et al.*, 2023). Using the same methods and GWAS data as described in the Baranova study, we however reassuringly arrived at an effect estimate similar to our main analysis (OR: 1.10, **ESM Table S6, ESM SNP data 9**), thus we were unable to replicate the larger Baranova estimate of OR 1.30. Results from a meta-analysis and an observational study also demonstrated a positive association (OR: 2.29 and HR: 2.35, respectively) between ADHD and T2D (Garcia-Argibay *et al.*, 2023). It must be mentioned that MR results are necessarily on the liability scale (i.e. per log-odds unit increase in genetic liability to ADHD) rather than the binary scale (ADHD yes/no), thus the observational estimate cannot be directly compared to our MR estimates.

We found evidence that BMI mediates the effect of ADHD on T2D. Multiple studies have demonstrated that ADHD liability is associated with an increased risk of obesity (Karhunen *et al.*, 2021; Nigg *et al.*, 2016) or higher BMI (Liu *et al.*, 2021). Garcia-Argibay *et al.* (2023) also found observational evidence of a mediating role of obesity. We extended the evidence that this mediating pathway is causal. Impaired inhibitory control and reward sensitivity that characterize ADHD could result in unhealthy, irregular eating habits (Cortese and Castellanos, 2014) thus leading to obesity. Given that obesity, or elevated BMI are thought to be the primary causes of T2D (Censin *et al.*, 2019; Sun *et al.*, 2022), the indirect pathway from ADHD to obesity/higher BMI to T2D might be the most relevant.

Furthermore, we found that part of the association between ADHD and T2D is driven by lower educational attainment, which is related to lower SES, and accordingly lower financial security, lower quality employment and less job security (Galobardes *et al.*, 2006a, 2006b). These SES-related risk factors are associated with T2D, potentially due to poorer nutrition, poorer health behaviours, less healthcare seeking and poorer access to (high quality) healthcare (Gavin *et al.*, 2024; Krishnan *et al.*, 2010; Zhang *et al.*, 2022). Therefore, associations between ADHD and T2D may not only be driven by educational attainment, but also partly be driven by the socio-economic context into which individuals with ADHD are sorted by the educational system (Schmengler *et al.*, 2023). Thus, ADHD related symptoms, such as forgetfulness, and difficulty in engaging and sustaining attention, could induce poor performance in school (Jangmo *et al.*, 2019). As a consequence, children with ADHD are more often assigned to lower educational tracks in selective educational systems, subsequently leading to lower educational attainment, illustrating the health-related selection into lower SES (Schmengler *et al.*, 2023).

Next to BMI and EA, our study suggests sedentary behaviour, measured by TV watching, is a mediator. Those with ADHD are observed to engage in more screen time (Ansari and Crosnoe, 2016), with dose-dependency on severity of ADHD (Montagni *et al.*, 2016; Vaidyanathan *et al.*, 2021). Possibly, ADHD people are prompted to watch TV or gaming to seek arousal, or to avoid social difficulties (Roberti, 2004; Vandewater *et al.*, 2005). Such sedentary behaviour could lead to increases in trunk and body fat percentage, thereby increasing risk of T2D (Li *et al.*, 2022a).

The mediation effects of the three pathways described above are not expected to be independent of each other, given the strong (genetic) correlations and potential causal relationships between BMI, EA and sedentary behaviour (Cassidy *et al.*, 2017; van de Vegte *et al.*, 2020; Zhang *et al.*, 2022). We therefore performed analyses in which we modelled combined mediation effects. These indeed yielded non-additive results, i.e. combined effects through all three mediators were smaller than the sum of the individual effects, corroborating overlap in mediation effects. Our MVMR results show that each individual mediator generally retains significant effects on T2D conditional on the other mediators, suggesting partially independent effects and thus incomplete overlap. We additionally found there that nearly half of the total effect remains unexplained by BMI, EA and TV watching. Other mediating pathways thus likely exist. A recent register-based study suggests the observed association between ADHD and T2D is largely explained by psychiatric comorbidities, with unhealthy behaviours (smoking and drinking), dietary habits and neurobiological abnormalities proposed as possible explanations (Garcia-Argibay *et al.*, 2023). Once sufficiently large GWAS studies on these potential additional mediators are available, it would be possible to assess their indirect effects through MR.

The difference of coefficients method returned a much lower estimate of proportion mediated by BMI than our main products method (16% vs 44%). Possibly, this is due to non-collapsibility of the odds ratio. The mediation literature recommends the product-of-coefficients method, but binary outcomes must have a low prevalence (i.e. $<$10%), so that the odds ratio approximates the linear risk ratio (Vanderweele and Vansteelandt, 2010). In case of common outcomes (i.e. prevalence $>$10%), estimates from the product-of-coefficients method and difference of coefficients method are unlikely to perfectly align (Carter *et al.*, 2021). In the present study, both methods agreed on mediation by BMI, EA and TV watching. Nevertheless, some caution is warranted with regard to the differing BMI estimates, as well as our estimates of combined proportion mediated, for which we necessarily used the difference method.

In sensitivity reverse MR analysis, we found surprising results suggestive of reverse causation, i.e. several of our candidate mediators (i.e. smoking, BMI, EA, TV watching) are suggested to cause ADHD. Such effects of smoking and EA on ADHD were also reported in another MR study (Soler Artigas *et al.*, 2023). There is evidence that physical exercise mitigates ADHD symptoms (Choi *et al.*, 2015; Rommel *et al.*, 2013) and some evidence that screen time reduces executive functioning (Liu *et al.*, 2022) and thus, some

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bidirectionality is possible. However, we find it highly unlikely that these factors cause onset of ADHD. A plausible explanation is that MR estimates (both in forward and reverse analyses) are affected by biased GWAS estimates induced by (spurious) gene-environment correlation (Quinn and D'Onofrio, 2020). Also, gene-trait associations are possibly mediated through the family environment due to assortative mating (partner choice based on similarity, resulting in non-random distribution of genetic variants) (Howe *et al.*, 2019), dynastic effects (effects of non-transmitted alleles that affect traits through the environment) (Kong *et al.*, 2018). Alternatively, reverse causation could be due to inherited alleles, i.e. parental EA and smoking, for instance, would affect offspring ADHD risk and severity of symptoms. Genetic propensity towards lower EA and smoking in individuals with ADHD could thus be inherited from the parents. Indeed, there is evidence that the above described phenomena could affect genetic studies into ADHD. One study found evidence that liability of earlier age at first sexual intercourse and of lower rate of past tobacco smoking in non-heavy smokers increasing the odds of ADHD (Soler Artigas *et al.*, 2023), similar to the chronologically implausible reverse effect of EA on ADHD in our study. These apparent reverse effects may be driven by dynastic effects, as literatures linked young parental age or maternal smoking with increased risk of ADHD in children (Huang *et al.*, 2018; Hvolgaard Mikkelsen *et al.*, 2017). Assortative mating is also likely in individuals with ADHD, with a sevenfold higher odds of ADHD in the partner (Nordsletten *et al.*, 2016). Studies comparing within-family with population-based GWAS estimates found that within-sibship estimates are smaller than population estimates, for educational attainment, cognitive ability, depressive symptoms and smoking, with a shrinkage in SNP effects that ranged from 19% (smoking) to 50% (depressive symptoms) (Howe *et al.*, 2022). Although the authors did not investigate ADHD, their results suggests that SNP-estimates of population-based GWAS on cognition and mental health could in part be confounded by demographic effects (population stratification, assortative mating) and indirect genetic effects. In contrast, one twin study investigated within- and between-family differences in ADHD polygenic score effects on ADHD symptoms found little difference (Selzam *et al.*, 2019). This suggests that for ADHD, confounding by demographic and indirect genetic effects is negligible. Given all the above, although there is currently limited evidence of bias in population-based GWAS on ADHD, we cannot exclude the possibility that ADHD SNP estimates are biased through these phenomena. Within-family analysis is thought to be largely robust against these effects (Brumpton *et al.*, 2020; Davies *et al.*, 2019). Therefore, sufficiently large within-family data (e.g. parent-offspring trios, between-sibling design), currently unavailable for ADHD, is needed to account for such potential sources of bias in GWASs and MR and further validate our findings.

Given the evidence for a causal effect of ADHD on T2D, it is to be expected that successful management of ADHD will reduce T2D risk either directly or through increasing EA, reducing BMI and promoting non-sedentary behaviour in individuals with ADHD. Based on large registry data, it has been shown that treatment with ADHD medication increases school grades as well as the probability of completing upper secondary education (Jangmo *et al.*, 2019), while discontinuation of ADHD medication was associated with a (small) decline in grades (Keilow *et al.*, 2018). Similarly, test scores were higher during periods on rather than off medication (Lu *et al.*, 2017). Collaborative school-home behavioural interventions may also benefit educational outcomes (Pfiffner *et al.*, 2013). With regard to reducing BMI, it is known that stimulant treatment reduces appetite, and thus, weight loss, in children with overweight or obesity and ADHD, stimulant treatment yields an additional benefit in terms of weight management (Fast *et al.*, 2021). Similarly, we already mentioned that physical exercise reduces ADHD symptoms (Choi *et al.*, 2015) with the added advantage that this may benefit weight lowering. Finally, it is implausible that stimulant treatment reduces sedentary behaviour and screen time, but behavioural interventions, although not specifically studied in individuals with ADHD, may provide effective treatment (Jones *et al.*, 2021). Finally, high BMI in individuals with ADHD could additionally be targeted through diet (e.g. replacing a 'Western-style' diet with a healthy diet) (Howard *et al.*, 2011; Millichap and Yee, 2012). It has also been reported that altering the metabolic profile via restriction and elimination diets will reduce both ADHD symptoms and BMI level (Pelsser *et al.*, 2011).

Previous MR studies that investigated mediation generally used IVW estimates, which relies on the strong assumption of absence of horizontal pleiotropy. Given that horizontal pleiotropy is likely to be pervasive (Hemani *et al.*, 2017), using IVW estimates might not always be appropriate. We therefore relied on the MR-MoE tool which uses a reproducible, pre-defined machine learning algorithm to identify the most appropriate models and thus most reliable univariable MR estimates that were then taken forward to mediation analysis. For the MVMR setting however, relatively few pleiotropy robust methods are available, and to our knowledge, no machine learning algorithm for prioritizing MVMR models exists. Thus, the MVMR-IVW estimates of direct effects we used for mediation analysis may be biased by pleiotropy, even though estimates from MVMR-Egger were largely consistent. Future study, simulation or otherwise, may investigate potential machine learning algorithms to prioritize MVMR models.

This is the first study that systematically explores mediating mechanisms in the relation between ADHD and T2D using MR methods. We used the most comprehensive large-scale GWAS data available to us, optimizing the power and precision of our study. Several limitations must be acknowledged. First, we already mentioned that gene-environment correlation, assortative mating and dynastic effects may bias GWASs and by that MR. This awaits GWASs that use within-family data. Second, MR may be biased by pleiotropic effects of SNPs, i.e. genetic variants influencing the outcome through other pathways than the exposure, which would be a violation of exclusion restriction criterion. Therefore, we compared estimates from a wide range of pleiotropy robust MR analyses, which generally and reassuringly showed consistency. Nevertheless, MR makes several assumptions that are strong and untestable, and thus MR results should be interpreted with caution. Third, the present study assumes the absence of exposure × mediator interaction, the investigation of which requires large-scale individual level data and is therefore not possible with summary level data. Four, conditional instrument strength for ADHD in MVMR was low ($F < 10$). Future, more powerful GWAS may identify stronger instruments for ADHD with which our MVMR results may be corroborated. Fifth, if any sample overlap existed between GWAS studies it may have biased MR estimates towards observational, possibly confounded, association estimates (Burgess *et al.*, 2016). These limitations illustrate that more evidence is needed to firmly establish causality, by triangulating with future observational and (quasi-)interventional studies.

We conclude that there is a possible causal relationship between liability of ADHD and T2D, in which ADHD liability causes higher

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T2D risk through higher BMI, more TV watching and lower EA. Intervention on these factors may have beneficial effects on reducing T2D risk in individuals with ADHD.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2045796024000593.

Availability of data and materials. GWAS data are publicly available through the MRC IEU Open GWAS database (https://gwas.mrcieu.ac.uk/). The analysis code can be shared upon request.

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Competing interests. The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Ethical standards. All summary data were extracted from published studies, which were approved by the institutional review committees in their respective studies. Therefore, no further sanction was required.

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