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Research article

Exploring the association between grip strength and adverse pregnancy and perinatal outcomes: A Mendelian randomization study

Yanpeng Wang [a,1], Yinzhen Zhang [a,1], Wenhai Zhao [b], Wenjun Cai [c], Changwei Zhao [b,*]

[a] Department of Traditional Chinese Medicine, Changchun University of Chinese Medicine, 130117, China
[b] Department of Orthopedics, The Affiliated Hospital to Changchun University of Chinese Medicine, 130021, China
[c] Department of Orthopedics, The Third Affiliated Hospital of Changchun University of Chinese Medicine, 130000, China

A R T I C L E I N F O

Keywords:
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A B S T R A C T

Background: Previous observational studies have demonstrated an association between grip strength and detrimental pregnancy and perinatal outcomes. However, the causality of this relationship remains uncertain.
Objective: This study aims to investigate if there is a causal relationship between grip strength and adverse pregnancy and perinatal outcomes, providing evidence to support active intervention for adverse pregnancy outcomes.
Study design: A two-sample Mendelian randomization method was used to select GWAS data from the UK Biobank and the FinnGen Biobank as data sources. The inverse variance weighting method was used as the main analysis method. The reliability of the results was verified through sensitivity analysis, including Cochran's Q test, MR-egger intercept regression analysis, leave-one-out analysis, and funnel plot. Independent queues are also used to verify the reliability of the results.
Results: The study demonstrated a significant positive correlation between genetically predicted hand grip strength and offspring birth weight, specifically left-hand grip strength ($\beta = 0.193$, 95 % CI: 0.099–0.286, $p = 0.0001$) and right-hand grip strength ($\beta = 0.310$, 95 % CI: 0.235–0.384, $p = 3.27E-16$). Sensitivity analysis indicated no horizontal multi-effect, and leave-one-out analysis along with the funnel plot showed no abnormalities. The verification queue also yielded similar results.
Conclusion: This study revealed a significant association between grip strength-related traits and offspring birth weight, suggesting a potential protective effect. Moreover, a negative predictive trend was observed for other adverse pregnancy outcomes. Modifying grip strength through an active lifestyle and continuous monitoring of pregnant women's grip strength may have implications for improving pregnancy outcomes. However, further research is warranted to investigate these findings more comprehensively.

* Corresponding author. 1478 Gongnong Road, Chaoyang District, Changchun City, Jilin Province, 130021, China.
E-mail address: zcw_1980@126.com (C. Zhao).
[1] These two authors equally contributed to this work.

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1. Introduction

Adverse pregnancy outcomes are pathological complications during pregnancy and childbirth that have both short-term and long-term impacts on the mother or baby. Despite significant research progress in identifying risk factors for adverse pregnancy outcomes in recent decades, the incidence of these complications remains high. They contribute to maternal, fetal, and neonatal mortality rates and pose a significant public health concern [1].

Grip strength serves as an objective and straightforward indicator of muscle strength [2] and reflects the overall nutritional status of the body [3]. Previous studies have demonstrated a relationship between grip strength and adverse pregnancy outcomes. A longitudinal study found a positive correlation between maternal hand grip strength and offspring birth weight [3]. Another prospective study suggested that the grip strength test could potentially predict gestational hypertension and preeclampsia [4], while a cross-sectional study found no association between grip strength and gestational diabetes mellitus [5]. However, observational studies are vulnerable to confounding factors and reverse causality, and traditional randomized controlled trials face limitations in experimental design and ethical considerations, often making them challenging to conduct. Mendelian randomization (MR) offers a novel approach to address these issues.

MR is a method that utilizes genetic variation as an instrumental variable to infer causal relationships between exposure factors and outcomes [6]. Because alleles are randomly assigned during mutation, this approach allows for minimizing the influence of confounding factors. MR has been widely employed in disease risk factor research with notable advancements [7–10]. In this study, we utilized the MR method to investigate the association between muscle strength and adverse pregnancy outcomes, aiming to provide evidence supporting active interventions for adverse pregnancy outcomes.

2. Research design and methods

2.1. Research design

In this study, we employed a two-sample MR method. We identified single nucleotide polymorphisms (SNPs) that are strongly associated with grip strength as instrumental variables (IVs). These IVs were utilized in MR analysis to investigate the causal relationship between hand grip strength and various outcomes, including offspring birth weight, spontaneous abortion, gestational hypertension, preeclampsia, and gestational diabetes. MR analysis requires adherence to three assumptions. Firstly, the instrumental variables must be closely associated with the exposure factor (hand grip strength). Secondly, it is necessary to ensure independence between the instrumental variable and the outcome. Thirdly, potential confounding factors that could influence the exposure-outcome pathway must be excluded. To bolster the robustness of our research findings, we employed various sensitivity analysis methods and employed independent datasets for validation.

2.2. Data source

Data on hand grip strength were obtained from the UK Biobank (UKBB), which included a total of 335,842 European individuals with measurements of both left and right hand grip strength. Information on spontaneous abortion, preeclampsia, gestational diabetes, and gestational hypertension was acquired from the FinnGen. The GWAS data on birth weight were retrieved from the UKBB. This study encompassed data from 261,932 individuals of European ancestry. The offspring birth weight data in the validation cohort were sourced from the Early Growth Genetics (EGG) consortium. This study encompassed 190,406 samples from the UKBB and 19,861 European blood samples from additional studies. We used the birth weight of offspring based on maternal effect as our validation cohort. Table 1 provides an overview of the essential details regarding the data sources.

Table 1
Data sources and basic information.

	Resource	Samplesize (case/control)	Number of SNPs	Ancestor
Exposure				
Right hand grip strength	Neale Lab	335,842	10,894,596	European
Left hand grip strength	Neale Lab	335,821	10,894,596	European
Outcome				
Brith weight	MRC-IEU	261,932	9,851,867	European
Spontaneous abortion	FinnGen	9113/89,340	16,379,138	European
Pregnancy hypertension	FinnGen	7686/115,893	16,379,784	European
Pre-eclampsia	FinnGen	3556/114,735	16,379,671	European
Ectopic pregnancy	FinnGen	3111/89,340	16,378,923	European
Gestational diabetes	FinnGen	5687/117,892	16,379,784	European
Verification queue				
Birth weight	EGG	210267	–	European

	Methods	nsnp	pval		MR egger_intercept	MR egger intercept_pval	Cochran's Q	Cochran's Q_pval
Exposure								
Left hand grip strength								
Outcome				**Beta(95%CI)**				
Birth weight	Inverse variance weighted	60	0.0001	0.193(0.099~0.286)	0.002	0.569	176.140	0.000
	MR Egger	60	0.7563	0.069(-0.364~0.502)				
	Weighted median	60	0.0022	0.152(0.055~0.249)				
Outcome				**OR(95%CI)**				
Ectopic pregnancy	Inverse variance weighted	58	0.7151	0.880(0.444~1.745)	0.001	0.964	53.882	0.593
	MR Egger	58	0.9032	0.820(0.034~19.748)				
	Weighted median	58	0.2203	0.550(0.212~1.430)				
Gestational diabetes	Inverse variance weighted	58	0.0748	0.631(0.381~1.047)	0.011	0.459	74.070	0.064
	MR Egger	58	0.2708	0.265(0.025~2.754)				
	Weighted median	58	0.1076	0.575(0.293~1.128)				
Pre-eclampsia	Inverse variance weighted	58	0.6089	0.864(0.495~1.510)	0.008	0.624	61.995	0.303
	MR Egger	58	0.5568	0.459(0.035~6.071)				
	Weighted median	58	0.7007	1.169(0.526~2.598)				
Pregnancy hypertension	Inverse variance weighted	58	0.0637	0.653(0.416~1.025)	0.032	0.019	70.241	0.112
	MR Egger	58	0.0076	0.059(0.008~0.437)				
	Weighted median	58	0.0413	0.536(0.294~0.976)				
Spontaneous abortion	Inverse variance weighted	58	0.0355	0.670(0.461~0.973)	0.016	0.150	76.370	0.044
	MR Egger	58	0.0647	0.194(0.035~1.068)				
	Weighted median	58	0.0145	0.526(0.315~0.880)				

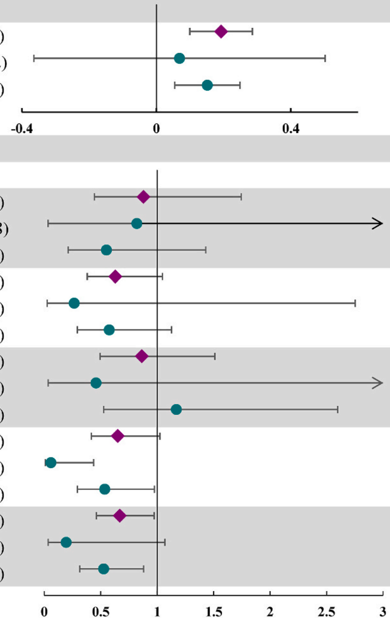

Fig. 1. MR analysis and sensitivity analysis results of the relationship between left hand grip strength, adverse pregnancy, and perinatal outcomes.

	Methods	nsnp	pval		MR egger_intercept	MR egger intercept_pval	Cochran's Q	Cochran's Q_pval
Exposure								
Right hand grip strength								
Outcome				**Beta(95%CI)**				
Birth weight	Inverse variance weighted	91	3.27E-16	0.310(0.235~0.384)	0.001	0.628	546.375	0.000
	MR Egger	91	0.1104	0.240(-0.052~0.531)				
	Weighted median	91	3.49E-11	0.266(0.188~0.345)				
Outcome				**OR(95%CI)**				
Ectopic pregnancy	Inverse variance weighted	98	0.2145	0.754(0.483~1.178)	-0.007	0.593	88.448	0.721
	MR Egger	98	0.8319	1.217(0.200~7.410)				
	Weighted median	98	0.2275	0.679(0.362~1.273)				
Gestational diabetes	Inverse variance weighted	98	0.0149	0.602(0.400~0.906)	0.021	0.070	123.697	0.035
	MR Egger	98	0.0192	0.137(0.027~0.703)				
	Weighted median	98	0.0796	0.609(0.349~1.060)				
Pre-eclampsia	Inverse variance weighted	98	0.8913	1.030(0.676~1.569)	0.009	0.463	112.752	0.131
	MR Egger	98	0.4978	0.552(0.100~3.052)				
	Weighted median	98	0.9638	1.014(0.545~1.889)				
Pregnancy hypertension	Inverse variance weighted	98	0.5717	0.907(0.647~1.271)	0.009	0.321	137.212	0.005
	MR Egger	98	0.2715	0.462(0.117~1.816)				
	Weighted median	98	0.8210	0.947(0.591~1.517)				
Spontaneous abortion	Inverse variance weighted	98	0.0392	0.736(0.550~0.985)	0.003	0.754	91.911	0.627
	MR Egger	98	0.4190	0.612(0.187~2.003)				
	Weighted median	98	0.0398	0.663(0.449~0.981)				

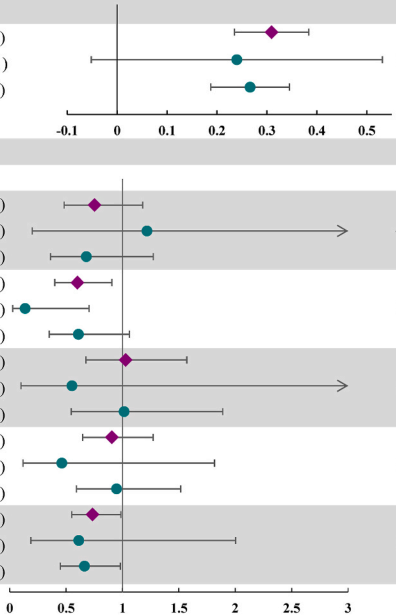

Fig. 2. MR analysis and sensitivity analysis results of the relationship between right hand grip strength, adverse pregnancy, and perinatal outcomes.

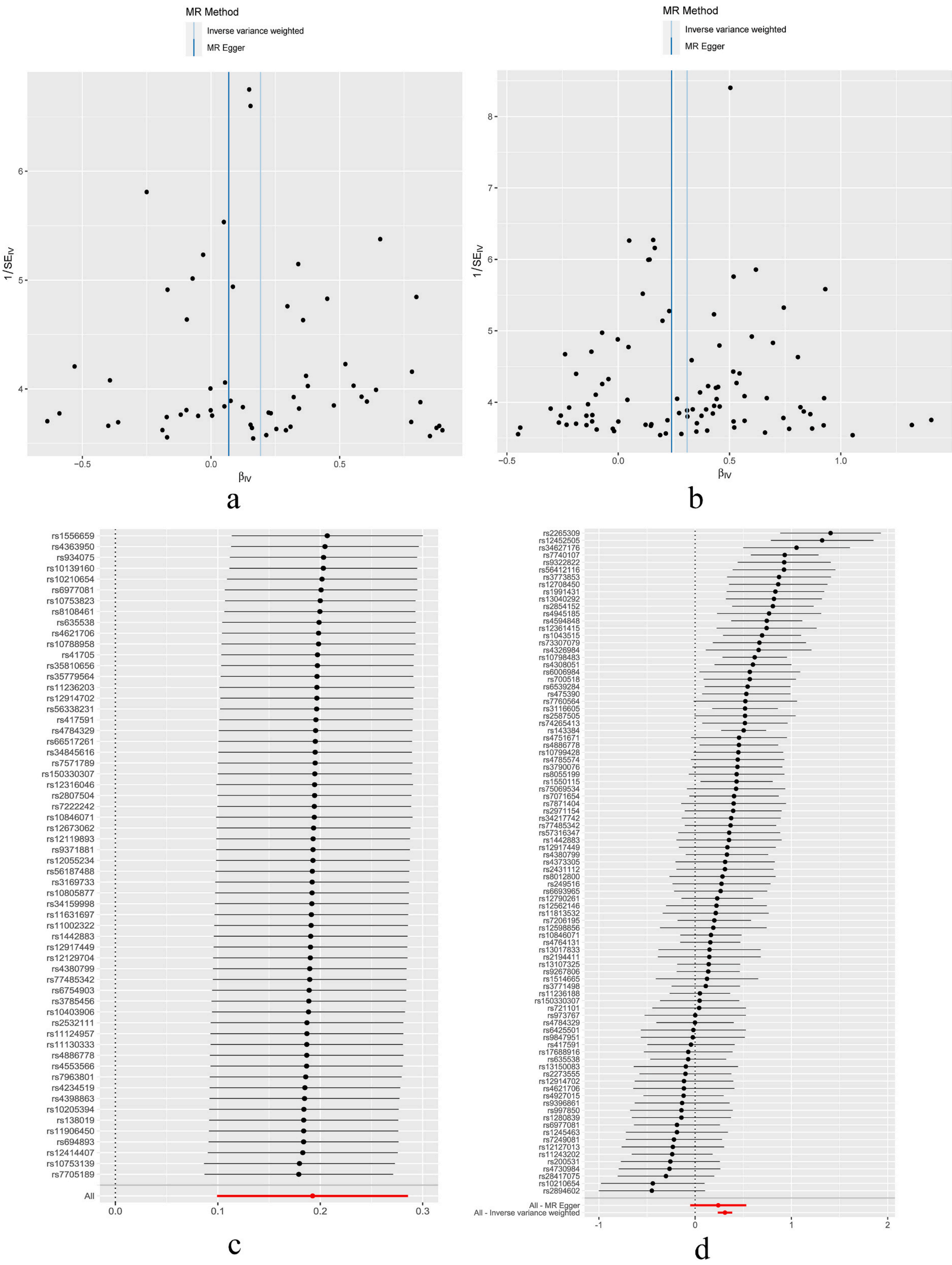

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Fig. 3. Funnel plot and leave-one-out plot for MR analysis of hand grip strength and offspring birth weight, a, Funnel plot for sensitivity analysis of left hand grip strength and offspring birth weight, b, Funnel plot for sensitivity analysis of right hand grip strength and offspring birth weight, c,A leave-one-out plot of sensitivity analysis of the relationship between left hand grip strength and offspring birth weight, d,A leave-one-out plot of sensitivity analysis of the relationship between right hand grip strength and offspring birth weight.

2.3. Extraction of IVs

We initially extracted SNPs that exhibited a significant association with hand grip strength ($P < 5 \times 10^{-8}$). Next, we utilized a spacing of 10 MB and a linkage disequilibrium threshold of $r^2 = 0.001$ to remove any potential confounding effects. Subsequently, we calculated the F value for each SNP and selected instrumental variables with an F value > 10 to ensure the exclusion of weak IVs. We obtained the relevant phenotypic information for each SNP using the online tool Phenoscnner, and excluded SNPs that were linked to BMI, smoking, drinking, education, and the outcomes of interest to minimize the impact of confounding factors. We further conducted analyses using MR-PRESSO to identify and eliminate potential outliers. The SNPs that remained after this selection process were deemed as the final IVs for estimation.

We observed a sample overlap between grip strength and offspring birth weight, with a sample overlap rate of 77.99 %. Previous studies [11,12] have indicated that, in two-sample MR analysis, aside from the MR-Egger method, other methodologies can be safely employed for analysis utilizing the same biological sample repository, such as the UKBB. If the correlation between gene exposure influenced by confounding factors and gene result estimation can be maintained at a low level, or if the variability of instrument strength is very high, MR-Egger analysis can be applied. Furthermore, we assessed the bias resulting from sample overlap using the online tool at https://sb452.shinyapps.io/overlap/[13]. The results indicate that the bias induced by the two exposures equals the MR estimates of 0.001, 0.001, respectively, suggesting that the sample overlap bias caused by other MR methods can be ignored.

2.4. Statistical analysis

Our primary analysis method was the inverse-variance weighting (IVW) method with random effects. This approach is based on the valid assumptions of all core MR assumptions. Additionally, we employed the MR-Egger and weighted median methods as complementary approaches to obtain more reliable estimates. We utilized MR-PRESSO to identify potential outliers that may impact the results. Furthermore, we performed a series of sensitivity analyses, including the Cochran's Q test, MR-Egger intercept regression analysis, leave-one-out analysis, and funnel plot. The Cochran's Q test assessed potential heterogeneity, with a significance level of $P < 0.05$ indicating the presence of heterogeneity. MR-Egger regression analysis can be employed to assess gene pleiotropy bias, with its regression intercept serving as an indicator of pleiotropy magnitude. A regression intercept closer to 0 suggests lower likelihood of gene pleiotropy. Leave-one-out analysis and funnel plots were employed to assess the reliability of the findings.

For binary outcomes including spontaneous abortion, gestational hypertension, preeclampsia, and gestational diabetes, we utilized odds ratios (OR) with 95 % confidence intervals (CI) to assess causality. Similarly, for estimating the causal effect of offspring birth weight, we employed β values with 95 % CI. All statistical analyses in this study were conducted using RStudio 2023.03.1, R 4.22, TwosampleMR, and MR-PRESSO packages. Following Bonferroni correction, a significance level of $P < 0.008$ (0.05/6) was considered statistically significant, while P values between 0.008 and 0.05 were considered nominally significant.

3. Results

3.1. IVs

After the screening process, a total of 60 IVs were used for left-hand grip strength, and 98 IVs were used for right-hand grip strength. These IVs explained 3.98 % and 7.08 % of the genetic variation in left-hand and right-hand grip strength, respectively. The F value of the selected IVs ranged from 15.3 to 86.4, ensuring the exclusion of weak instrumental variables. Details of the included IVs can be found in the supplementary file.

3.2. MR results

The results of the MR analysis revealed a significant positive correlation between left-hand grip strength, right-hand grip strength, and birth weight using the primary analytical methods. Specifically, for left-hand grip strength, the β coefficient was 0.193 (95 % CI: 0.099–0.286, p = 0.0001), and for right-hand grip strength, it was 0.310 (95 % CI: 0.235–0.384, p = 3.27E-16). Consistently, the results from the other two analytical methods corroborated this trend, and the weighted median model also demonstrated a significant positive correlation: for left-hand grip strength, the β coefficient was 0.152 (95 % CI: 0.055–0.249, p = 0.0022), and for right-hand grip strength, it was 0.266 (95 % CI: 0.188–0.345, p = 3.49E-11). Additionally, we observed a nominally significant negative correlation between two-hand grip strength and spontaneous abortion, as well as between right-hand grip strength and gestational diabetes (refer to Figs. 1 and 2).

In the sensitivity analysis, the MR analysis of two-hand grip strength and birth weight did not show any horizontal pleiotropic effects. However, there was a high degree of heterogeneity between the SNPs (Figs. 1 and 2). Since we employed the random effects model as our main analysis method, the level of heterogeneity was deemed acceptable [14]. Additionally, the leave-one-out analysis

	Methods	nsnp	pval	Beta(95%CI)	MR egger_intercept	MR egger intercept_pval	Cochran's Q	Cochran's Q_pval
Outcome								
Birth weight								
Exposure								
Left hand grip strength	Inverse variance weighted	61	0.0462	0.122(0.002~0.242)	-0.002	0.659	96.820	0.002
	MR Egger	61	0.3947	0.246(-0.317~0.810)				
	Weighted median	61	0.0104	0.191(0.045~0.338)				
Right hand grip strength	Inverse variance weighted	99	0.0033	0.138(0.046~0.229)	-0.001	0.689	163.817	3.47E-05
	MR Egger	99	0.2523	0.207(-0.145~0.560)				
	Weighted median	99	0.0017	0.181(0.068~0.294)				

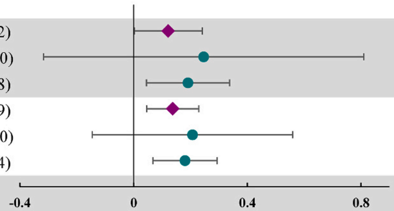

Fig. 4. MR analysis and sensitivity analysis results of two-handed grip strength and offspring birth weight based on the validation cohort.

(Fig. 3a and b) and funnel plot (Fig. 3c and d) did not reveal any evident abnormalities.

3.3. Queue verification

The results of queue verification are depicted in Fig. 4. Analysis of individual cohorts revealed a significant correlation between left hand grip strength, right hand grip strength, and offspring birth weight (Left hand: $\beta = 0.122$, 95 % CI: 0.002–0.242, $p = 0.0462$; Right hand: $\beta = 0.138$, 95 % CI: 0.046–0.229, $p = 0.0033$). All three analytical approaches consistently yielded results in the same direction, aligning with our primary analysis findings, while sensitivity analysis results also suggest the absence of horizontal pleiotropy.

4. Discussion

4.1. Principal findings

Our findings demonstrate a correlation between grip strength and offspring birth weight. Specifically, a one-standard-deviation (SD) increase in left grip strength corresponds to a 0.193 SD increase in offspring birth weight. Similarly, a one-SD increase in right grip strength correlates with a 0.310 SD increase in offspring birth weight. These findings were additionally validated through sensitivity analysis and cohort verification.

4.2. Results

Previous studies have primarily focused on examining the association between individual birth weight and subsequent grip strength [15–18]. However, limited research has explored the relationship between maternal grip strength and offspring birth weight. Zerazniewicz et al. [19] conducted a longitudinal study involving 95 healthy pregnant women to investigate this relationship. They measured the maximum grip strength of both hands during early, middle, and late stages of pregnancy while controlling for factors such as economic status, educational level, and occupation. The study revealed a positive correlation between maternal hand grip strength and birth weight of the offspring, highlighting the significant impact of grip strength during the second trimester of pregnancy. Our study produced similar findings. It is widely accepted that offspring birth weight is closely associated with the maternal nursing and nutritional status during pregnancy. A higher nutritional status is typically linked to increased birth weight. Hand grip strength serves as a fundamental indicator of overall body nutrition [3]. Furthermore, maternal hormone levels have been shown to influence offspring birth weight [20], and changes in hormone levels have also been connected to muscle strength [21], particularly in women. Grip strength is recognized as a predictor for cardiovascular and cerebrovascular diseases [22] as well as low back pain [23] in pregnant women. Improved grip strength equates to enhanced physical functioning, which forms a vital basis for mitigating adverse pregnancy outcomes.

Our research also demonstrates that grip strength exhibits a negative correlation with spontaneous abortion and gestational diabetes. Additionally, in relation to other outcomes, all three models indicate a broad range of negative correlations, thereby suggesting the significant predictive value of grip strength in identifying adverse pregnancy outcomes. Given that grip strength can be modified by lifestyle factors such as exercise [24] and diet [25], targeted interventions aimed at enhancing grip strength and overall health status during pregnancy preparation or pregnancy itself hold substantial importance in preventing adverse pregnancy outcomes.

4.3. Clinical implications

Our study investigates the association between grip strength and adverse pregnancy and perinatal outcomes, which has been supported by previous observational studies. Therefore, it suggests that continuous monitoring and active intervention of grip strength in pregnant and postpartum women may help reduce the occurrence of adverse outcomes. This finding can provide guidance for prenatal examinations and the development of related health policies. However, future large-scale cohort studies are needed to further demonstrate this relationship.

4.4. Research implications

Despite conducting qualitative research on the relationship between grip strength and adverse pregnancy and perinatal outcomes, it is important to note that due to the characteristics of the MR study design, we are unable to quantify the specific relationship between the two throughout the maternal pregnancy cycle. Therefore, we cannot determine whether changes in grip strength within a specific cycle will have a significant correlation with pregnancy outcomes. This aspect requires further investigation in future research.

4.5. Strengths and limitations

The strength of our research lies in the utilization of MR, which helps minimize the influence of confounding factors and determine the causal relationship between exposure factors and outcomes. However, our study also possesses several limitations. Firstly, the use of IVW as the primary analysis method raises concerns regarding potential bias due to weak instruments and the winner's curse. Additionally, there is a degree of sample overlap. While our analysis indicates a small resulting bias, it is recommended to employ more robust sensitivity assessment methods like MRlap [26] in future studies to enhance the accuracy of the causal effect estimation.

Secondly, due to constraints within the original dataset, a hierarchical analysis was unfeasible, thereby restricting the depth of our research discussion and the potential for expansion. Thirdly, the predominantly European sample selection limits the generalizability of our findings to other ethnic backgrounds. Furthermore, the explained proportion of genetic variation by grip strength is modest, and the inclusion of numerous SNPs in the MR analysis introduces considerable heterogeneity, potentially impacting the results. Nevertheless, the IVW estimation of random effects was utilized to mitigate any bias. Lastly, our study investigates the impact of grip strength on offspring birth weight over the entire period, suggesting the need for a larger observational study to explore this relationship within specific periods.

5. Conclusion

In summary, our study found that grip strength-related traits had a positive impact on offspring birth weight and showed a negative predictive trend for other adverse pregnancy outcomes. Therefore, promoting an active lifestyle and implementing continuous monitoring of grip strength in pregnant women may be valuable in modifying adverse pregnancy outcomes.

Ethical approval and consent to participate

This study uses publicly available GWAS data, therefore no additional ethical approval is required. All of the studies and consortia accessed in the present study were approved by their respective ethics committee, and the subjects from all the cohorts provided written informed consent.

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Data availability statement

This study used publicly available GWAS data, which can be found in the FinnGen (https://www.finngen.fi/en) and UK Biobank (https://www.ukbiobank.ac.uk/).All of the data generated or analyzed during this study are included in this article and its supplementary material files. Data will be made available on request.

CRediT authorship contribution statement

Yanpeng Wang: Writing – original draft, Conceptualization. **Yinzhen Zhang:** Writing – original draft, Conceptualization. **Wenhai Zhao:** Software, Data curation. **Wenjun Cai:** Visualization, Investigation. **Changwei Zhao:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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This study was carried out using data from the UK Biobank(https://www.ukbiobank.ac.uk/) and FinnGen (https://www.finngen.fi/en), and we would like to express our gratitude to the participants and researchers involved in this project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33465.

Abbreviations

MR Mendelian Randomization
SNP Single Nucleotide Polymorphism
IV Instrumental Variable
IVW Inverse variance weighting

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