四川大学学报（医学版） 2025，56（3）：697－710
J Sichuan Univ（Med Sci）

在线全文

·论 著·

Association Between Low Birth Weight and Dementia Risk: A Large-scale Prospective Study

YU Xinyue[1, 2, 3], *XUE Qingping*[1], *LI Jingyi*[1, 2], *ZHANG Peiqi*[1, 2], *OUYANG Qingqing*[1, 2], *LUO Xiaoxue*[1, 2], *HE Qian*[1, 2], *WANG Yongliu*[1, 2], *ZHAO Ying*[1, 2], *HE Xiangwang*[2], *LI Fan*[2], *YANG Yunhaonan*[2△], *PAN Xiongfei*[2, 3, 4, 5△]. 1. *Department of Epidemiology and Biostatistics, School of Public Health, Chengdu Medical College, Chengdu 610599, China*; 2. *Section of Epidemiology and Population Health, Key Laboratory of Birth Defects and Related Diseases of Women and Children of the Ministry of Education & Sichuan Provincial Key Laboratory of Children's Medication, West China Second University Hospital, Sichuan University, Chengdu 610041, China*; 3. *Department of Gynecology and Obstetrics, West China Second University Hospital, Sichuan University, Chengdu 610041, China*; 4. *West China Biomedical Big Data Center, West China Hospital, Sichuan University, Chengdu 610041, China*; 5. *Shuangliu Institute of Women's and Children's Health, Shuangliu District Maternal and Child Health Hospital, Chengdu 610200, China*

△ Corresponding author, YANG Yunhaonan, E-mail: yunhaonanyang@scu.edu.cn; PAN Xiongfei, E-mail: pxiongfei@scu.edu.cn

[Abstract] **Objective** To investigate the association between birth weight and dementia risk and the mediating roles of chronic diseases, and to assess potential biological pathways underlying the birth weight-associated dementia risk based on large-scale proteomics. **Methods** We used data from 279 743 participants aged 40 to 69 years enrolled in the UK Biobank. Birth weight was categorized into low birth weight (≤ 2 500 g), normal birth weight (2 500-3 999 g), and macrosomia (≥ 4 000 g). Multivariable Cox proportional hazards regression models were used to assess the associations between birth weight categories and all-cause dementia and its subtypes (Alzheimer's disease and vascular dementia). Proteomics analyses were conducted to identify proteins and the potential pathways involved. **Results** Low birth weight was associated with higher risks for all-cause dementia and its subtypes. The hazard ratios were 1.18 (95% CI, 1.08-1.30) for all-cause dementia, 1.14 (95% CI, 1.00-1.31) for Alzheimer's disease, and 1.22 (95% CI, 1.01-1.48) for vascular dementia. A non-linear relationship was observed between birth weight and dementia risk (P for nonlinearity < 0.001). Certain cardiometabolic diseases in middle-aged adults, such as diabetes, stroke, hypertension, and dyslipidemia, played a significant mediating role in the relationship between low birth weight and dementia risk, with the mediation proportion being 6.3% to 15.8%. Proteomic analyses identified 21 proteins linked to both low birth weight and all-cause dementia risk, which were significantly enriched in the pathways for viral protein interaction with cytokines and cytokine receptors, adipocytokine signaling, and cytokine-cytokine receptor interaction. **Conclusion** Low birth weight is positively associated with dementia risk. Cardiometabolic diseases in middle-aged adults may mediate the relationship between low birth weight and dementia risk. A number of proteins and the associated pathways underscore the relationship between low birth weight and dementia risk.

[Key words] Birth weight Dementia Proteomics Alzheimer's disease Vascular dementia

低出生体重与痴呆风险关联的大型前瞻性研究

余欣月[1, 2, 3]，薛清萍[1]，李静怡[1, 2]，张珮琦[1, 2]，欧阳青青[1, 2]，骆晓雪[1, 2]，何 倩[1, 2]，王永柳[1, 2]，赵 颖[1, 2]，何享旺[2]，李 凡[2]，杨云浩男[2△]，潘雄飞[2, 3, 4, 5△]

1. 成都医学院公共卫生学院 流行病学与生物统计教研室（成都 610599）；2. 四川大学华西第二医院 出生缺陷及妇女儿童相关疾病教育部重点实验室 儿童药物四川省重点实验室 流行病学与人群健康实验室（成都 610041）；3. 四川大学华西第二医院 妇产科（成都 610041）；4. 四川大学华西医院 华西生物医学大数据中心（成都 610041）；5. 成都市双流区妇幼保健院双流妇幼医学研究中心（成都 610200）

【摘要】 **目的** 探讨低出生体重与痴呆风险的关联及慢性疾病的中介作用，揭示基于蛋白质组学的潜在生物学通路。**方法** 基于英国生物银行（UK Biobank，UKB）279 743名40～69岁研究对象数据，按出生体重分为低出生体重儿（≤2 500 g）、正常出生体重儿（2 500-3 999 g）和巨大儿（≥4 000 g），采用多变量Cox回归分析出生体重与全因痴呆及亚型（阿尔茨海默病、血管性痴呆）风险的关联，并结合蛋白质组学筛选蛋白及相关通路。**结果** 低出生体重与全因痴呆及其亚型

△ 通信作者，杨云浩男，E-mail：yunhaonanyang@scu.edu.cn；潘雄飞，E-mail：pxiongfei@scu.edu.cn

出版日期：2025-05-20

的风险相关：全因痴呆的风险比为1.18 (95%CI 1.08, 1.30)、阿尔茨海默病为1.14 (95%CI 1.00, 1.31)、血管性痴呆为1.22(95%CI 1.01, 1.48)。出生体重与痴呆风险存在非线性关联($P_{非线性}$<0.001)。中年心血管代谢疾病(糖尿病、脑卒中、高血压、高血脂)在低出生体重和全因痴呆关联中发挥中介效应，中介比例为6.3%～15.8%。蛋白质组学鉴定出21个同时与低出生体重和痴呆关联的蛋白，富集于病毒蛋白与细胞因子及其受体的相互作用通路、脂肪因子信号通路、细胞因子-细胞因子受体相互作用通路。**结论** 低出生体重与痴呆风险呈正相关，中年心血管代谢性疾病可能介导这一关联。多种蛋白及相关通路在低出生体重和痴呆风险关联中发挥作用。

【关键词】 出生体重 痴呆 蛋白质组学 阿尔茨海默病 血管性痴呆

Dementia is a major health issue around the world. The number of people with dementia is projected to increase from 57.4 million cases globally in 2019 to 152.8 million cases in 2050[1]. Despite the significant burden of dementia, the impact of early-life factors on future dementia risk remains largely unclear[2]. Given the heightened vulnerability of the brain during the prenatal stage, it is crucial to investigate the role of prenatal factors in dementia development.

Birth weight is a major prenatal factor that predicts future disease risk. Lower birth weight has been reported to associate with smaller brain size, poorer cognitive function, and a higher risk of dementia[3-4], while higher birth weight has shown associations with larger brain volume and better cognitive function in older populations[5-6]. Although existing research indicates a possible link between birth weight and risk of dementia, the findings were still inconsistent due to differences in study design, sample selection, and adjustment for potential confounding factors such as socioeconomic status, educational attainment, and other environmental or genetic factors[7-8]. In addition, the precise mechanisms through which birth weight influences dementia risk remain to be fully elucidated. Chronic diseases, such as diabetes, hypertension, and stroke, along with inflammatory markers and glycolipid metabolites, may act as potential mediators in this relationship. Proteomics, as a high-throughput analytical technique, facilitates a comprehensive assessment of protein expression, functional characteristics, and regulatory mechanisms, providing valuable insights into the pathophysiological processes underlying complex diseases.[9-10]. Existing research has highlighted the critical roles of specific proteins in cognitive regulation and neurodegenerative diseases[11]. However, previous studies have not incorporated proteomic analysis when examining the relationship between birth weight and dementia.

To address the knowledge gap, we aimed to investigate the prospective association between birth weight and dementia risk, and the mediating roles of chronic diseases in the UK Biobank. In addition, we utilized large-scale proteomics data in this cohort to assess potential biological pathways underlying the birth weight-dementia risk.

1 MATERIALS AND METHODS

1.1 Study population

We used data from the UK Biobank, a large-scale prospective cohort study that aimed to investigate genetic and lifestyle factors associated with common diseases in middle-aged and elderly populations[12]. Between 2006 and 2010, the UK Biobank recruited 502 364 participants aged 40 to 69 years[13]. All study participants provided electronic informed consent, and the study received necessary ethical approvals. At the baseline phase of the study, participants provided information on demographics, early-life exposures (e.g., birth weight), and lifestyle factors through touchscreen questionnaires and physical examinations. Biological samples, including blood, were collected from participants. Subsequently, participants have been followed over time through linkages to national databases, including health records, death registries, and primary care records. In our main association analyses, we excluded the following participants: 1) individuals with data missing for birth weight (n = 222 080); 2) individuals with birth weight beyond mean ± 5 standard deviation (SD, n = 335); 3) individuals with dementia at baseline (n = 206). Baseline onset of dementia was determined by comparing the date of first dementia diagnosis with the baseline assessment date. A total of 279 743 individuals were included in the final analysis (Due to space limitation, further details are provided in Supplementary Figure S1 available online at the publisher's website [https://ykxb.scu.edu.cn/]).

1.2 Exposure assessment

The exposure of interest was birth weight obtained at baseline through self-reported questionnaire responses. Participants were asked to report their birth weight. In the primary analyses, birth weight was classified into three

categories: low birth weight (≤2 500 g), normal birth weight (2 500-3 999 g), and macrosomia (≥ 4 000 g). In secondary analyses, birth weight was also treated as a continuous variable to assess potential nonlinearity.

1.3 Outcome assessment

The primary outcome was incident all-cause dementia, which included Alzheimer's disease (ICD-10: F00, G30), vascular dementia (ICD-10: F01, I67), and other or unspecified types of dementia (ICD-10: F02, F03) (Due to space limitation, further details are provided in Supplementary Table S1 available online at the publisher's website [https://ykxb.scu.edu.cn/]). Secondary outcomes included incident Alzheimer's disease, and vascular dementia. The duration of follow-up was calculated as the time (in years) from birth to dementia diagnosis, or loss to follow-up, or the study's censoring date (follow up ending on September 1, 2023), which ever came first.

1.4 Covariate assessment

Several covariates were assessed, including baseline age, sex, ethnicity, Townsend deprivation index, education level, household income, employment status, smoking status, alcohol intake, physical activity, sleep duration, nap frequency, Apolipoprotein E (APOE) ε4 carrier status (carrier/non-carrier based on genetic variants rs429358 and rs7412, defining ε4ε4, ε4ε3, or ε4ε2 genotypes), body mass index (BMI), and baseline comorbidities (including diabetes, coronary heart disease, stroke, hypertension, and dyslipidemia).

Ethnicity was categorized into White and non-White groups. The Townsend deprivation index, an aggregate measure of socioeconomic deprivation incorporating factors such as unemployment, household overcrowding, and lack of home or car ownership, was categorized into three groups: low (Quintile 1), moderate (Quintiles 2-4), and high (Quintile 5). Higher scores reflect greater levels of material deprivation and resource scarcity[14]. Education level was classified as higher (college/university degree or other professional qualifications) or lower. Household income, reflecting pre-tax average total household income, was grouped into < £18 000, £18 000-£30 999, £31 000-£51 999, and ≥ £52 000 categories. Employment status was categorized as employed, retired, and other (unemployed, caring for home/family, unable to work due to illness or disability, unpaid/voluntary work, full/part-time student, or no response). Smoking status was defined as "never", "previous", and "current". Alcohol intake was categorized into "never", "less than 3 times a month", "1-4 times a week" and "daily or almost daily". Total physical activity (TPA) was assessed using a modified version of the International Physical Activity Questionnaire (IPAQ). TPA was calculated as a continuous score by weighting walking, moderate activity, and vigorous activity with 3.3, 4, and 8 metabolic equivalents (METs), respectively[15]. This score was then categorized into three groups: low (< 800 MET-min/week), moderate (800-2 400 MET-min/week), and high (≥ 2 400 MET-min/week). To measure sleep duration, participants were asked: "About how many hours sleep do you get in every 24 h?" Total hours per day of sleep duration was divided into three categories according to tertiles: low (0-6 h), moderate (7 h) and high (≥ 8 h)[16]. The daytime napping frequency was determined based on the participant's response to the question "Do you have a nap during the day?" The response options included never/rarely, sometimes, usually, and prefer not to answer. The option "prefer not to answer" was categorized as missing data. BMI was calculated as body weight in kilograms divided by height in meters squared, and was categorized into < 25, 25-30, and ≥ 30 kg/m^2. Baseline diabetes, stroke, coronary heart disease, hypertension, and dyslipidemia were determined based on ICD-10 criteria (Due to space limitation, further details are provided in Supplementary Table S1 available online at the publisher's website [https://ykxb.scu.edu.cn/]) and self-reported diagnoses.

1.5 Plasma proteomics

We obtained data from the UK Biobank Pharma Proteomics Project, where protein measurements were conducted using the Proximity Extension Assay by Olink. Protein levels were reported as log-transformed Normalized Protein eXpression (NPX) values. Detailed information on the normalization procedures is available in the UK Biobank Olink Normalization Guide. The proteomic dataset comprised measurements of 2 923 proteins from 53 013 participants. Among the 279 743 participants in our study cohort, 250 766 lacked proteomic data. Proteomic data preprocessing adhered to the standardized protocol established by the UK Biobank, employing principal component analysis (PCA), median, and interquartile range

(IQR) metrics to detect and exclude outliers[17]. We excluded 39 participants due to NPX outliers, resulting in 28 938 participants being included in the final proteomic analyses.

1.6 Statistical analysis

Prior to analyses, we performed imputation for missing data in 158 738 participants using the multiple imputation by chained equations method. Different imputation approaches were applied based on variable types: predictive mean matching for continuous variables, logistic regression for binary variables, ordered logistic regression for ordered categorical variables, and multinomial logistic regression for unordered categorical variables.

First, we described the baseline characteristics of the study population. Continuous variables were presented as mean (standard deviation, SD) if normally distributed, or as median (IQR), if skewed. Categorical variables were expressed as frequency (percentage). To compare differences in characteristics across birth weight categories, we used analysis of variance (ANOVA) and chi-square test for continuous and categorical variables, respectively.

Next, we used multivariable Cox proportional hazards regression models to examine the association between birth weight categories and dementia risk. The proportional hazards assumption was tested using Schoenfeld residuals[18]. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the association between birth weight and dementia risk with adjustment for covariates in a stepwise manner: 1) Model 1 contained no covariates; 2) Model 2 was adjusted for age and sex; and 3) Model 3 was further adjusted for ethnicity, education level, household income, employment status, Townsend deprivation index, smoking, alcohol intake, physical activity, sleep duration, napping habits, APOE ε4 carrier status, and BMI groups at baseline. We also investigated the non-linear relationship between birth weight (as a continuous variable) and dementia risk using restricted cubic splines-based models with three knots.

To ensure the robustness of our findings, we conducted two sensitivity analyses. First, we calculated E-values to quantify the minimum risk ratio an unmeasured confounder would need to have with both the exposure and the outcome to fully explain the observed associations[19]. Larger E-values suggest greater robustness to potential unmeasured confounding. Second, to address potential recall bias in self-reported birth weight, we implemented a matrix-based correction method for polytomous exposure misclassification, accounting for both differential and non-differential misclassification[20]. Based on external validation studies[21] and assumed sensitivity parameters, we specified a misclassification probability matrix for non-dementia participants as:

$$P=\begin{bmatrix} Sen_{Low} & 1-Sen_{Low} & 0 \\ 0.027 & 0.886 & 0.087 \\ 0 & 1-Sen_{Macro} & Sen_{Macro} \end{bmatrix}$$

where Sen_{Low} and Sen_{Macro} represent the classification sensitivities of low birth weight and macrosomia, respectively, with values ranging from 0.5 to 0.9. To reflect reduced classification accuracy among dementia cases, we scaled all three sensitivities by ρ (range: 0.8 to 1), where ρ=1 indicates non-differential misclassification. Other matrix elements were proportionally adjusted to ensure each row summed to one. Using Bayes' theorem, we calculated posterior probabilities of true exposure categories and generated 50 completed datasets with imputed true exposure categories. Adjusted HRs were pooled using standard multiple imputation techniques.

We conducted subgroup analyses by sex, age, BMI, and APOE ε4 carrier status, and effect modification was formally assessed by including an interaction term of these variables and birth weight categories in the Cox model. We conducted mediation analyses to examine whether baseline chronic diseases, including diabetes, coronary heart disease, stroke, hypertension, dyslipidemia, and overweight or obesity (defined as BMI $\geqslant$ 25 kg/m^2) mediated the relationship between birth weight and dementia risk. We first estimated the total effect of birth weight group on incident dementia, adjusting for the aforementioned covariates. Next, we extended the adjusted model to include individual mediators to estimate the direct effect. The indirect effect was calculated as the difference between the total and direct effects. The mediation proportion was calculated as (indirect effect/total effect) × 100%. The 95% CIs and *P* values were derived using 1,000 bootstrap resamples.

Third, we explored proteins that were associated with birth weight and dementia. Both birth weight and protein levels (NPX values) were standardized to *Z* scores. We used

linear regression models to assess the association between birth weight and each protein, and used Cox proportional hazards regression models to assess the association of differential proteins with dementia risk. To account for potential false positives arising from multiple comparisons, we applied the false discovery rate (FDR) correction using the Benjamini-Hochberg method[22]. For both regression models, a dual threshold was applied to determine statistical significance: associations were deemed significant only if the absolute value of the regression coefficient (β) for the protein exceeded 0.1 and the FDR-adjusted P value was below 0.05. Protein-protein interaction analyses of the identified proteins were conducted using STRING, with an interaction confidence threshold of 0.4. A k-means clustering algorithm (with four clusters) was applied to identify groups of connected proteins. Pathway enrichment analyses were conducted using the KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway database. We performed the principal component analysis (PCA) on all identified proteins and those within the enriched pathways. To examine whether overall protein distribution patterns differed by dementia status, we used permutation multivariate analysis of variance (PERMANOVA), based on a Euclidean distance matrix with 999 permutations. To investigate potential mechanisms underlying the association between low birth weight and dementia risk, we conducted mediation analysis using two categories of protein-related variables. The first category included individual proteins significantly associated with both low birth weight and all-cause dementia. The second category comprised the first principal component (PC1) derived from specific protein sets, including: (1) all proteins significantly associated with low birth weight and all-cause dementia; and (2) proteins involved in each enriched KEGG pathway. Due to the relatively small sample size for the proteomic analysis, the statistical power may be insufficient. Therefore, we employed a two-stage approach for the mediation analysis. In the first stage, we calculated the total effect of birth weight on all-cause dementia across the entire population. In the second stage, we computed the indirect effect in the subset of individuals with available protein data. The direct effect was defined as the difference between the total effect and the indirect effect, while the mediation proportion was calculated as (indirect effect/total effect) × 100%. We derived 95% CIs and P values using 1 000 bootstrap resamples.

Statistical analysis for this study was performed using R Studio version 4.3.0, with a two-tailed P value of < 0.05 considered statistically significant. We used the *mice* package for imputation of missing data and *clusterProfiler* package for the KEGG enrichment analyses.

2 RESULTS

2.1 Baseline characteristics

Of 279 743 participants, mean age was 55.2 years (SD, 8.1) and 61.0% were female. 28 601 (10.2%) had low birth weight and 37 154 (13.2%) had macrosomia at birth (Table 1).

Table 1　Baseline characteristics of study participants by birth weight categories

Characteristic	Total	Low birth weight	Normal birth weight	Macrosomia	P^a
Number of participants	279 743	28 601	213 988	37 154	
Age/yr., mean (SD)	55.2 (8.1)	56.4 (8.0)	54.9 (8.1)	56.1 (8.2)	< 0.001
Sex/case (%)					< 0.001
Male	109 016 (39.0)	8 215 (29.1)	81 321 (38.0)	19 480 (52.4)	
Female	170 727 (61.0)	20 386 (70.9)	132 667 (62.0)	17 674 (47.6)	
Ethnicity/case (%)					< 0.001
Non-white	7 066 (2.5)	1 004 (3.5)	5 363 (2.5)	699 (1.9%)	
White	272 677 (97.5)	27 597 (96.5)	208 625 (97.5)	36 455 (98.1)	
Educational attainment/case (%)					< 0.001
High	177 628 (63.5)	16 520 (57.8)	137 882 (64.4)	23 226 (62.5)	
Low	102 115 (36.5)	12 081 (42.2)	76 106 (35.6)	13 928 (37.5)	
Average total household income/case (%)					< 0.001
< £ 18 000	56 186 (20.1)	7 222 (25.3)	41 271 (19.3)	7 693 (20.7)	
£ 18 000- £ 30 999	68 073 (24.3)	7 627 (26.7)	51 282 (24.0)	9 164 (24.7)	
£ 31 000- £ 51 999	76 395 (27.3)	7 265 (25.4)	59 249 (27.7)	9 881 (26.6)	
⩾ £ 52 000	79 089 (28.3)	6 487 (22.7)	62 186 (29.1)	10 416 (28.0)	

(The table continues on the next page.)

Table 1 Baseline characteristics of study participants by birth weight categories (continued)

Characteristic	Total	Low birth weight	Normal birth weight	Macrosomia	P^a
Employment status/case (%)					< 0.001
Working	175 020 (62.6)	16 196 (56.6)	136 543 (63.8)	22 281 (60.0)	
Retired	81 132 (29.0)	9 570 (33.5)	59 600 (27.9)	11 962 (32.2)	
Other	23 591 (8.4)	2 835 (9.9)	17 845 (8.3)	2 911 (7.8)	
Townsend deprivation index/case (%)[b]					< 0.001
Low	56 569 (20.2)	5 298 (18.5)	43 815 (20.5)	7 456 (20.1)	
Moderate	167 368 (59.8)	16 753 (58.6)	128 375 (60.0)	22 240 (59.9)	
High	55 806 (19.9)	6 550 (22.9)	41 798 (19.5)	7 458 (20.1)	
Smoking status/case (%)					< 0.001
Never	159 787 (57.1)	17 209 (60.2)	123 187 (57.6)	19 391 (52.2)	
Previous	90 635 (32.4)	8 272 (28.9)	68 705 (32.1)	13 658 (36.8)	
Current	29 321 (10.5)	3 120 (10.9)	22 096 (10.3)	4 105 (11.0)	
Alcohol intake/case (%)					< 0.001
Never	19 570 (7.0)	2 582 (9.0)	14 423 (6.7)	2 565 (7.0)	
Less than 3 times a month	64 139 (22.9)	7 778 (27.2)	48 562 (22.7)	7 799 (21.0)	
1-4 times a week	141 075 (50.4)	13 766 (48.1)	108 566 (50.7)	18 743 (50.4)	
Daily or almost daily	54 959 (19.6)	4 475 (15.6)	42 437 (19.8)	8 047 (21.7)	
TPA groups/case (%)					< 0.001
Low	76 418 (27.3)	7 950 (27.8)	58 640 (27.4)	9 828 (26.5)	
Moderate	97 916 (35.0)	9 837 (34.4)	75 303 (35.2)	12 776 (34.4)	
High	105 409 (37.7)	10 814 (37.8)	80 045 (37.4)	14 550 (39.2)	
Sleep groups/case (%)					< 0.001
Low	67 447 (24.1)	7 434 (26.0)	50 894 (23.8)	9 119 (24.5)	
Normal	192 586 (68.8)	18 772 (65.6)	148 428 (69.4)	25 386 (68.3)	
High	19 710 (7.0)	2 395 (8.4)	14 666 (6.9)	2 649 (7.1)	
Nap frequency/case (%)					< 0.001
Never/rarely	165 101 (59.0)	15 968 (55.8)	127 933 (59.8)	21 200 (57.1)	
Sometimes	101 864 (36.4)	11 195 (39.1)	76 719 (35.9)	13 950 (37.5)	
Usually	12 778 (4.6)	1 438 (5.0)	9 336 (4.4)	2004 (5.4%)	
APOE ε4 carrier/case (%)					0.222
Yes	79 282 (28.3)	8 137 (28.5)	60 485 (28.3)	10 660 (28.7)	
No	200 461 (71.7)	20 464 (71.5)	153 503 (71.7)	26 494 (71.3)	
Baseline coronary heart disease/case (%)					< 0.001
Yes	5 339 (1.9)	747 (2.6)	3 713 (1.7)	879 (2.4)	
No	274 404 (98.1)	27 854 (97.4)	210 275 (98.3)	36 275 (97.6)	
Baseline diabetes/case (%)					< 0.001
Yes	12 467 (4.5)	1 937 (6.8)	8 901 (4.2)	1 629 (4.4)	
No	267 276 (95.5)	26 664 (93.2)	205 087 (95.8)	35 525 (95.6)	
Baseline stroke/case (%)					< 0.001
Yes	8 367 (3.0)	1 233 (4.3)	5 953 (2.8)	1 181 (3.2)	
No	271 376 (97.0)	27 368 (95.7)	208 035 (97.2)	35 973 (96.8)	
Baseline hypertension/case (%)					< 0.001
Yes	71 784 (25.7)	9 179 (32.1)	53 298 (24.9)	9 307 (25.0)	
No	207 959 (74.3)	19 422 (67.9)	160 690 (75.1)	27 847 (75.0)	
Baseline dyslipidemia/case (%)					< 0.001
Yes	7 687 (2.7)	1 106 (3.9)	5 441 (2.5)	1 140 (3.1)	
No	272 056 (97.3)	27 495 (96.1)	208 547 (97.5)	36 014 (96.9)	
BMI groups/case (%)					< 0.001
< 25 kg/m^2	95 814 (34.3)	9 609 (33.6)	75 879 (35.5)	10 326 (27.8)	
25-30 kg/m^2	115 832 (41.4)	11 449 (40.0)	88 339 (41.3)	16 044 (43.2)	
⩾ 30 kg/m^2	68 097 (24.3)	7 543 (26.4)	49 770 (23.3)	10 784 (29.0)	

BMI: body mass index; SD: standard deviation; TPA: total physical activity. [a] *P* values were derived using either analysis of variance or the chi-square test. [b] The Townsend deprivation index, an aggregate measure of socioeconomic deprivation incorporating factors such as unemployment, household overcrowding, and lack of home or car ownership, was categorized into three groups: low (Quintile 1), moderate (Quintiles 2-4), and high (Quintile 5).

Compared to study participants with normal birth weight, those with low birth weight were more likely to be female, while those with macrosomia were more likely to be male ($P < 0.001$). In addition, both participants with low birth weight and macrosomia were more likely to have low education, low income, and high Townsend deprivation index ($P < 0.001$). They were also more likely to have chronic diseases at baseline, including diabetes, coronary heart disease, stroke, hypertension, and dyslipidemia, and overweight or obesity (BMI ⩾ 25 kg/m^2) ($P < 0.001$).

2.2 Association between birth weight and dementia

During a follow-up of 19 562 577 person years, 4 085 cases of all-cause dementia, 1828 cases of Alzheimer's disease, and 889 cases of vascular dementia were recorded. Low birth weight was associated with 18% (HR, 1.18; 95% CI: 1.08, 1.30), 14% (HR, 1.14; 95% CI: 1.09, 1.31), and 22% (HR, 1.22; 95% CI: 1.01, 1.48) higher risks of all-cause dementia, Alzheimer's disease, and vascular dementia, respectively (Table 2). However, macrosomia was not associated with risks of all-cause dementia and its subtypes. Consistently, regression models based on restricted cubic splines showed a nonlinear relationship between birth weight and all-cause dementia and Alzheimer's disease (P for non-linearity < 0.001) (Figure 1). We conducted two sensitivity analyses to understand the impact of unmeasured

Table 2　Association of birth weight with risk of all-cause dementia and its subtypes

Factors	Normal birth weight	Low birth weight HR (95% CI)	Macrosomia HR (95% CI)
All-cause dementia			
Cases/person years	2 884/14 902 848	564/2 030 471	637/2 629 258
Model 1	1	1.21 (1.10, 1.32)	1.06 (0.94, 1.16)
Model 2	1	1.25 (1.15, 1.37)	1.04 (0.95, 1.13)
Model 3	1	1.18 (1.08, 1.30)	1.01 (0.92, 1.10)
Alzheimer's disease			
Cases/person years	1 277/1 490 284	248/2 030 471	303/2 629 258
Model 1	1	1.18 (1.04, 1.36)	1.13 (1.00, 1.28)
Model 2	1	1.20 (1.05, 1.38)	1.13 (0.99, 1.28)
Model 3	1	1.14 (1.00, 1.31)	1.10 (0.97, 1.25)
Vascular dementia			
Cases/person years	635/1 490 284	129/2 030 471	125/2 629 258
Model 1	1	1.25 (1.04, 1.51)	0.94 (0.78, 1.14)
Model 2	1	1.32 (1.09, 1.60)	0.88 (0.73, 1.07)
Model 3	1	1.22 (1.01, 1.48)	0.84 (0.69, 1.01)

HR: hazard ratio.

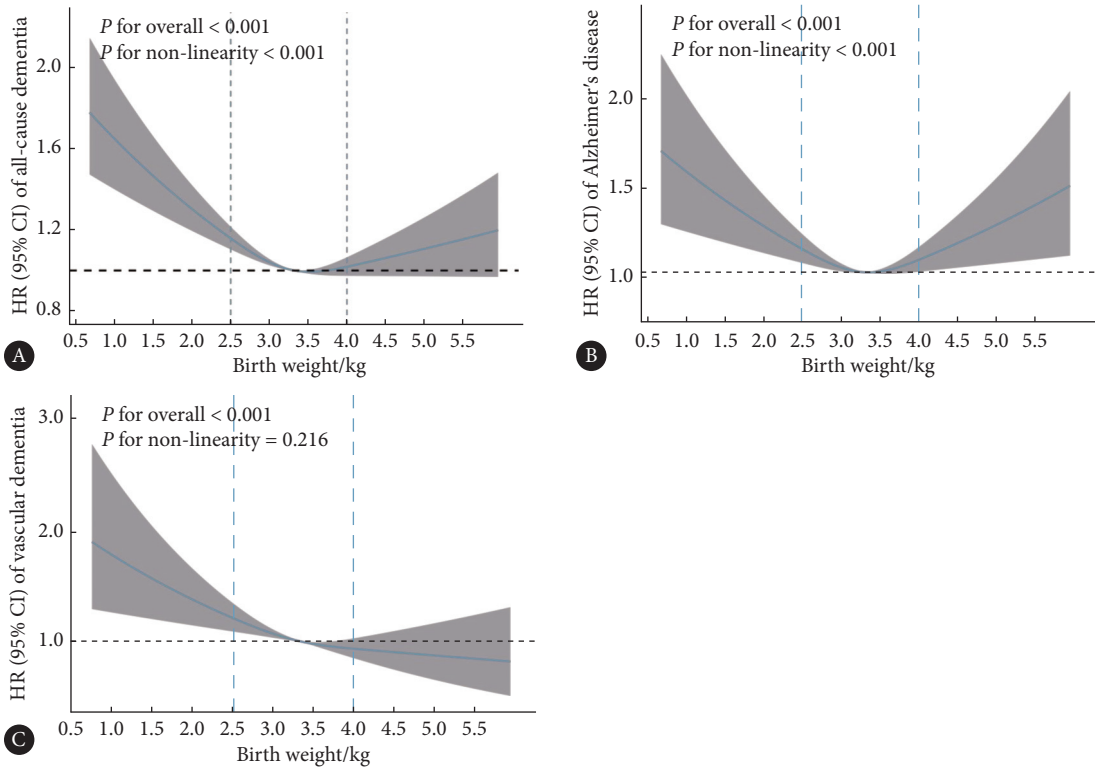


Fig 1　Association between birth weight and dementia using restricted cubic splines-based regression

HR: hazard ratio. A, Association with all-cause dementia. B, Association with Alzheimer's disease. C, Association with vascular dementia.

confounding and recall bias on the main results. For the observed associations between low birth weight and dementia outcomes, the E-values were 1.64 (95% CI limit: 1.37) for all-cause dementia, 1.54 (1.05) for Alzheimer's disease, and 1.74 (1.08) for vascular dementia. For macrosomia, the E-values were 1.11 (95% CI limit: 1.00) for all-cause dementia, 1.43 (1.00) for Alzheimer's disease, and 1.67 (1.00) for vascular dementia. These findings suggested that associations with low birth weight, particularly for vascular dementia, were relatively robust to unmeasured confounding, while associations with macrosomia, especially for all-cause dementia, were more susceptible to even weak confounding factors. In addition, our misclassification adjustment analysis revealed that the associations of low birth weight and macrosomia with all-cause dementia were underestimated across various non-differential misclassification scenarios (Due to space limitation, further details are provided in Supplementary Figure S2 available online at the publisher's website [https://ykxb.scu.edu.cn/]). When recall accuracy decreased in the dementia group, low birth weight remained a more robust risk factor for all-cause dementia. Based on these results, participants with macrosomia were excluded from subsequent analyses, which specifically focused on comparing disease risk between individuals with low birth weight and those with normal birth weight.

The positive associations between low birth weight and dementia and its subtypes were noted in most subgroups (Figure 2). For all-cause dementia, the association was stronger in individuals without APOE ε4, compared to those with APOE ε4 (1.34 vs. 1.08, *P* for interaction = 0.025). For vascular dementia, the association was stronger in individuals with normal weight in middle adulthood, compared to those with overweight (BMI 25-30 kg/m^2) or obesity (BMI ⩾ 30 kg/m^2) (1.62 vs. 1.28 vs. 0.95, *P* for interaction = 0.026).

Mediation analyses showed that cardiometabolic diseases (diabetes, stroke, hypertension, and dyslipidemia) in middle adulthood could mediate the association between low birth weight and all-cause dementia (Table 3). The mediation proportion ranged between 6.3% and 15.8%, with diabetes showing the strongest mediation effect. Coronary heart disease and obesity did not show a statistically significant mediation effect (*P* = 0.180 and 0.234).

2.3 Proteomics analyses

Of the 279 743 participants, 28 938 with proteomic data were comparable to those without proteomic data, although they were slightly older and were more likely to have a high Townsend deprivation index (Due to space limitation, further details are provided in Supplementary Table S2 available online at the publisher's website [https://ykxb.scu.edu.cn/]). Among the 28 938 participants, 602 were diagnosed with all-cause dementia. 139 proteins were identified as significantly associated with low birth weight

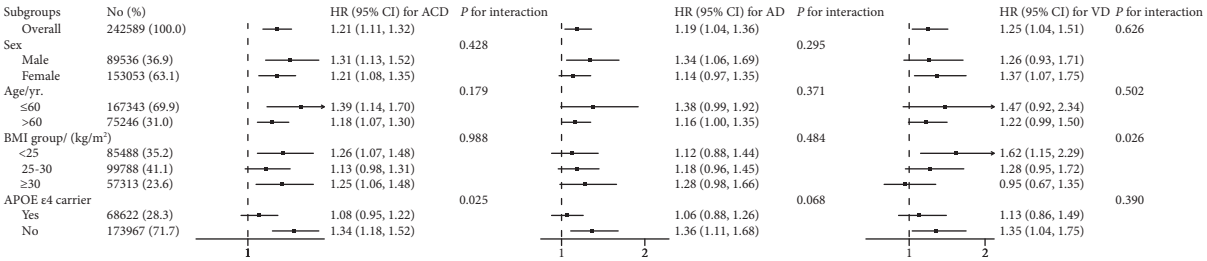


Fig 2 Subgroup analyses for the association between low birth weight and dementia risk across different subgroups

ACD: all-cause dementia; AD: Alzheimer's disease; BMI; body mass index; HR: hazard ratio; VD: vascular dementia.

Table 3 Mediation effects of chronic diseases on the association between low birth weight and risk of all-cause dementia

Mediator	Direct effect	Indirect effect	Mediation proportion	*P*
Diabetes	0.041 (0.012, 0.068)	0.008 (0.006, 0.010)	15.8% (9.1%, 39.2%)	0.002
Stroke	0.042 (0.014, 0.070)	0.006 (0.004, 0.008)	12.1% (6.1%, 31.7%)	0.002
Hypertension	0.043 (0.014, 0.071)	0.005 (0.004, 0.007)	10.5% (5.8%, 27.4%)	0.002
Dyslipidemia	0.045 (0.016, 0.073)	0.003 (0.002, 0.005)	6.3% (2.8%, 17.1%)	0.002

(β > 0.1 and FDR-adjusted P < 0.05), of which the top 10 proteins, ranked by β values, were SEMA3F, SERPINF1, LILRA5, FSTL3, NPDC1, PENK, BSG, CD59, CD99L2 and CST3 (Figure 3). In addition, 138 proteins were significantly associated with all-cause dementia, of which 116 showed positively associations and 22 showed negative associations. The top 10 proteins were NEFL, GFAP, GDF15, PLAUR, LTBP2, FGL1, SSC4D, CSF1, MMP3 and CCN5. 21 proteins were associated with both low birth weight and all-cause dementia. PCA of these proteins revealed that the first principal component (PC1) and the second principal component (PC2) explained 48.0% and 5.9% of the variance. The PERMANOVA analysis showed a significant difference in the distribution of 21 proteins between participants with and without all-cause dementia (P = 0.001, R^2 = 0.003 9) (Due to space limitation, further details are provided in Supplementary Figure S3 available online at the publisher's website [https://ykxb.scu.edu.cn/]).

Among the 21 identified proteins, GDF15 exhibited the strongest mediation effect, with a mediation proportion of 41.1% (Figure 3). Several other proteins, including PILRA (11.3%), PLAUR (14.2%), SPINK1 (10.7%), and TFF3 (13.1%), also showed notable mediation effects. We conducted protein–protein interaction and clustering analyses using the STRING database. Twelve proteins formed distinct interaction clusters enriched in pathways

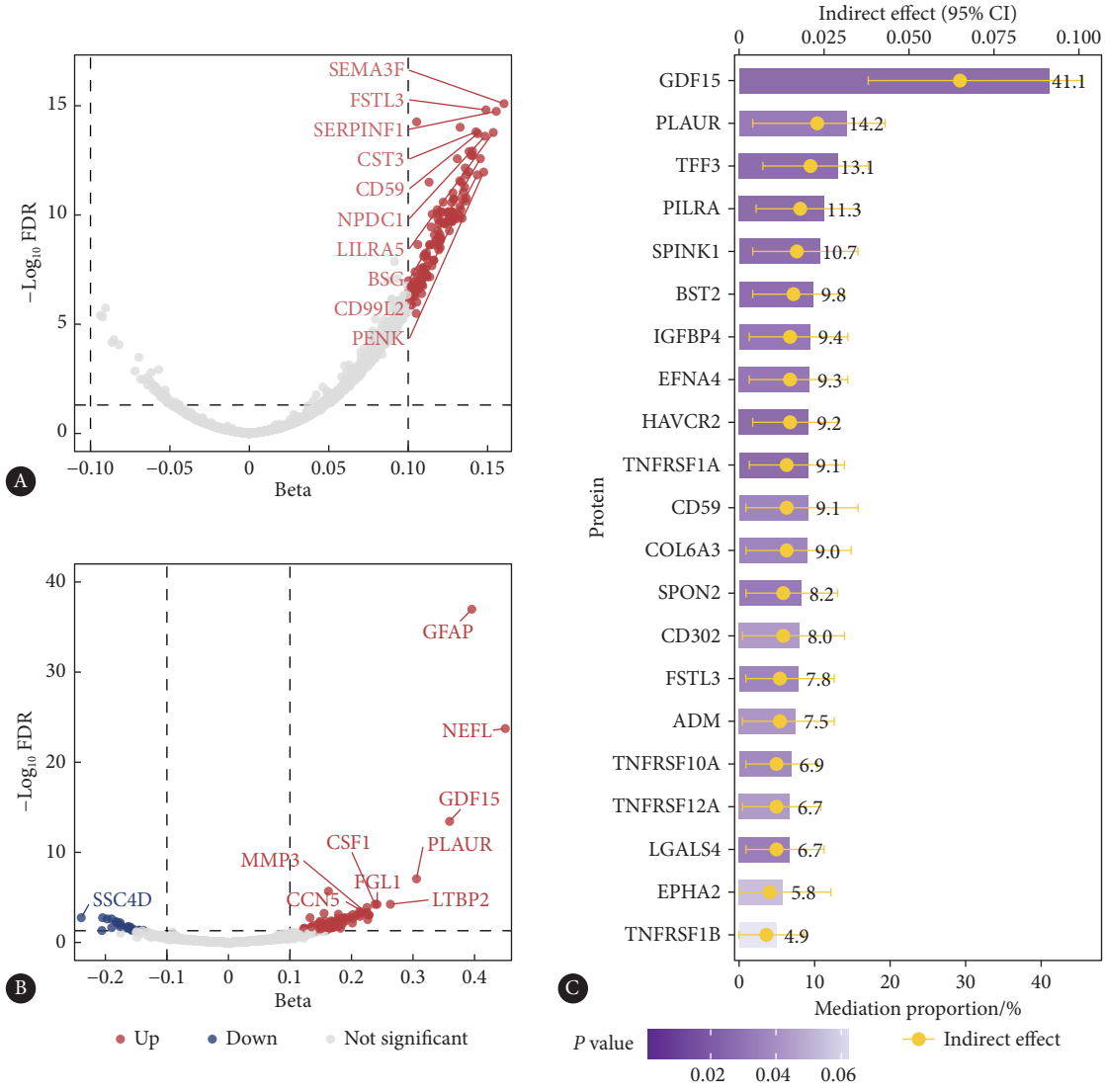
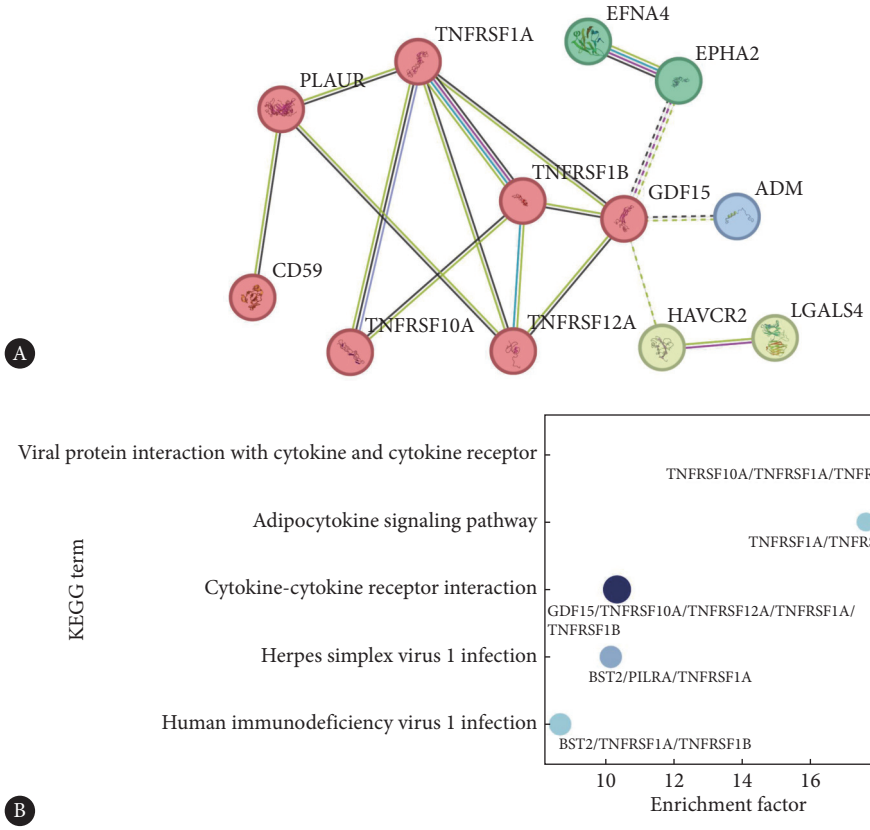


Fig 3 Proteins associated with low birth weight and all-cause dementia

FDR: false discovery rate. A, Volcano plot for 139 proteins associated with low birth weight. The names of the top 10 proteins with the largest absolute Beta values are presented. B, Volcano plot for 138 proteins associated with all-cause dementia. The names of the top 10 proteins with the largest absolute Beta values are presented. C, Mediating effects of 21 shared proteins in the association between low birth weight and all-cause dementia.

related to death receptor activity (CD59, PLAUR, TNFRSF1A, TNFRSF1B, TNFRSF10A, TNFRSF12A, and GDF15), as well as EPHA-mediated growth cone collapse and transmembrane ephrin receptor activity (EFNA4 and EPHA2; Figure 4). These results suggest that the identified pathway modules are interconnected, with GDF15 acting as a hub mediating interactions between them. KEGG pathway enrichment analyses identified five pathways associated with low birth weight and dementia risk, of which the viral protein interaction with cytokine and cytokine receptor (VPICCR), adipocytokine signaling pathway (ASP), and cytokine-cytokine receptor interaction (CCRI, Figure 4). The PC1 of 21 identified proteins mediated 19.9% of association between low birth weight and all-cause dementia (Figure 4). Similarly, the PC1 for proteins within each of the three important pathways CCRI, VPICCR, and ASP mediated 19.1%, 10.4%, and 7.8% of the low birth weight-dementia association.



C

Mediator	Direct effect	Indirect effect	Proportion mediated	*P* value
21 proteins	0.128 (0.031, 0.219)	0.032 (0.014, 0.056)	19.9% (8.2%, 52.7%)	<0.001
VPICCR	0.143 (0.049,0.230)	0.017 (0.004, 0.031)	10.4% (2.8%, 28.8%)	<0.001
ASP	0.147 (0.051, 0.234)	0.012 (0.002, 0.027)	7.8% (1.0%, 24.9%)	0.014
CCRI	0.129 (0.032, 0.219)	0.030 (0.013, 0.053)	19.1% (7.4%, 59.8%)	<0.001

Fig 4 Protein–protein interaction, pathway, and mediation analyses of 21 identified proteins

ASP: adipocytokine signaling pathway; CCRI: cytokine-cytokine receptor interaction; PC: principal component; PCA: principal component analysis; VPICCR: viral protein interaction with cytokine and cytokine receptor. A, STRING network of 4 protein–protein interaction clusters (indicated by node colors), with non-clustered orphan proteins removed; B, KEGG pathway enrichment analysis of the proteins identified; C, mediation effects of PC1 derived from PCA of the proteins identified and enriched pathways on the association between low birthweight and risk of all-cause dementia.

3 DISCUSSION

In this large-scale prospective study, we observed that low birth weight was associated with higher risks of dementia and its subtypes. Chronic conditions in middle adulthood, including diabetes, stroke, hypertension, and dyslipidemia, exhibited moderate mediation effects on the relationship between low birth weight and dementia risk. Furthermore, we identified 21 proteins that were linked to both low birth weight and dementia. These proteins and

their associated pathways also mediated the link between low birth weight and dementia risk. Our findings underscore the potential association between low birth weight and dementia risk, mediated through chronic conditions and mechanistic pathways in middle adulthood. This highlights the significance of adopting a life-course perspective to better understand and mitigate dementia risk.

Our study found a positive association between low birth weight and the risk of dementia. Consistent with our work, the Atherosclerosis Risk in Communities study, conducted in the United States, among 10 789 dementia-free participants aged 45-64 showed that individuals in the low birth weight group had a 1.2-fold higher risk of developing dementia compared to those in the moderate birth weight group[23]. Similarly, the Swedish Twin Registry in 35 191 twins also demonstrated a positive association between low birth weight and dementia risk[3]. This association was also supported by other evidence for cognitive decline in adults with low birth weight. Evidence linking low birth weight to specific dementia subtypes has been scarce. Nevertheless, our prospective study revealed strong positive associations with both Alzheimer's disease and vascular dementia, indicating that the detrimental effects of low birth weight could be linked to the shared mechanisms for dementia subtypes[24]. In contrast, we did not find an association between macrosomia and dementia, which was supported by evidence that larger birth weight is linked to more brain tissue reserve in older life[5]. The adverse impact of low birth weight on dementia and cognitive decline may be due to its long-term effects on chronic conditions, such as metabolic diseases that are also risk factors for dementia[25]. The mediating roles of these conditions should thus be explored in population studies.

In our study, a few chronic conditions in middle adulthood exhibited significant mediation effects in the association between low birth weight and dementia risk. There is a substantial body of evidence linking low birth weight with cardiometabolic diseases in adulthood[26]. Our study confirmed the positive association between low birth weight and cardiometabolic diseases such as diabetes, hypertension, and stroke, as well as the subsequent progression to dementia, thereby underscoring the lifelong health implications of low birth weight. The mediation effect by cardiometabolic diseases could be explained by a few potential distinct mechanisms. Low birth weight was reported to closely associate with structural and functional abnormalities in the cerebrovascular system, which may contribute to the occurrence of stroke[27]. Brain damage caused by stroke, particularly in the hippocampus and other regions critical for cognitive function, may accelerate cognitive decline and subsequently heighten the risk of developing dementia[28-29]. Stroke-induced activation of brain inflammation also accelerates brain aging, thus increasing the risk of developing dementia[30]. Low birth weight could be linked to insulin resistance, which may affect brain function through metabolic disturbances and poor blood glucose control[31-32]. These findings highlight the complex role of cardiometabolic diseases in linkling low birth weight to dementia.

As few studies elucidated potential molecular mechanisms underlying the association between birth weight and dementia, we conducted population-based proteomic analyses. We identified 21 proteins and related pathways that may mediate the association between low birth weight and dementia. These findings are hypothesis-generating and may guide future research on the link between early fetal growth and dementia. Among these proteins, GDF15 exhibited the strongest mediating role in the low birth weight-dementia link, and acted as a hub in the protein-protein interaction network. GDF15 has been implicated in neuroinflammatory processes and cellular stress responses that may contribute to neurodegeneration[33]. Consistently, previous studies showed that elevated GDF15 levels were significantly associated with cognitive impairment and an increased risk of dementia[34-35]. Although direct evidence linking low birth weight and GDF15 remains limited, GDF15 has been extensively studied and established as a critical regulator in energy metabolism and obesity-related disorders[36-37]. Our protein-protein interaction analysis revealed interconnected clusters primarily related to death receptor activity and ephrin receptor signaling. We explored the collective role of the identified 21 proteins using KEGG pathway enrichment analyses, and determined a few protein pathways such as viral protein interaction with cytokine and cytokine receptor, adipocytokine signaling pathway, and cytokine-cytokine receptor interaction. Both

the 21 proteins and these pathways also quantitatively mediated the relationship, which suggests that the relationship between birth weight and dementia may involve multiple molecular mechanisms. Although current evidence has not directly established a clear association of the viral protein interaction with cytokine and cytokine receptor pathway and the cytokine-cytokine receptor interaction pathway with the development of dementia, several proteins within the pathways (such as GDF15[38], TNFRSF12A[39], and TNFRSF1A[40]) can exert pro-inflammatory or anti-inflammatory effects. Given that chronic inflammation is considered as a significant risk factor for dementia[41-42], it is hypothesized that these proteins may influence the pathogenesis of dementia by modulating inflammatory responses. However, further research and evidence are needed to validate this hypothesis. The adipocytokine signaling pathway highlights the potential contribution of adipose tissue dysregulation to the progression of dementia. Although evidence supporting the adipocytokine signaling pathway is relatively limited, adipocytokines may indirectly influence neurodegenerative diseases by modulating systemic or localized inflammatory responses[43]. The three pathways suggest that low birth weight could impact neurological health and potentially exacerbate neurodegenerative changes through specific cytokines and metabolic pathways. Notably, the 21 identified proteins and their associated pathways accounted for less than 20% of the association between low birth weight and dementia, indicating that other unidentified factors also play a significant role in linking birth weight to dementia risk. To achieve a more comprehensive understanding, future studies should incorporate additional biological and clinical data to validate these findings.

The study has significant strengths, including its prospective design, large sample size, and detailed characterization of participants. However, several limitations must be acknowledged. First, birth weight was self-reported, thus introducing potential recall bias that may affect accuracy of our findings. In particular, the measurement of birth weight did not account for gestational age, leaving preterm status not accounted for in the analyses. However, our sensitivity analysis of recall bias still confirmed that low birth weight remained a robust risk factor for all-cause dementia. Second, as an observational study, it cannot establish causal relationships due to the potential influence of unmeasured confounding factors. Certain maternal factors such as maternal hypertension were not collected and accounted for in the association analyses for low birth weight and dementia. Our sensitivity analysis for unmeasured confounding also suggests that caution should be taken in interpreting the findings. While we explored proteomics for this association, the link should be further validated through mechanistic studies to elucidate the pathways. Third, the study predominantly enrolled middle-aged or older white individuals, limiting its generalizability to other populations. Future studies should explore this relationship across diverse ethnic groups.

In conclusion, our study demonstrated positive associations between low birth weight and all-cause dementia, including its subtypes. This relationship may be mediated by cardiometabolic conditions in middle adulthood and mechanistically explained by 21 proteins and their associated pathways. These findings underscore the critical role of early-life development in shaping neurodevelopmental outcomes in adulthood.

* * *

Author Contribution YU Xinyue is responsible for conceptualization, formal analysis, visualization, writing--original draft, and writing--review and editing. XUE Qingping is responsible for data curation, LI Jingyi, ZHANG Peiqi, and OUYANG Qingqing are responsible for validation and writing--review and editing. LUO Xiaoxue and WANG Yongliu are responsible for writing--review and editing. HE Qian and ZHAO Ying are responsible for visualization. HE Xiangwang is responsible for formal analysis and methodology. YANG Yunhaonan is responsible for data curation, formal analysis, methodology, validation, visualization, and writing--review and editing. PAN Xiongfei is responsible for conceptualization, methodology, project administration, supervision, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

Declaration of Conflicting Interests PAN Xiongfei is a member of the Junior Editorial Board of the journal. All processes involved in the editing and reviewing of this article were carried out in strict compliance with the journal's policies and there was no inappropriate personal involvement by the author. Other than this, all authors declare no competing interests.

References

[1] GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public

Health, 2022, 7(2): e105-e125. doi: 10.1016/S2468-2667(21)00249-8.
[2] WIEGERSMA AM, BOOTS A, LANGENDAM M W, *et al*. Do prenatal factors shape the risk for dementia? A systematic review of the epidemiological evidence for the prenatal origins of dementia. Soc Psychiatry Psychiatr Epidemiol, 2023. doi: 10.1007/s00127-023-02471-7.
[3] McNEIL C J, HABOTA T, SANDU A L, *et al*. The influence of birth weight, socio-economic status, and adult health on brain volumes during ageing. Neuroepidemiology, 2024, 14: 1-9. doi: 10.1159/000541918.
[4] MOSING M A, LUNDHOLM C, CNATTINGIUS S, *et al*. Associations between birth characteristics and age-related cognitive impairment and dementia: A registry-based cohort study. PLoS Med, 2018, 15(7): e1002609. doi: 10.1371/journal.pmed.
[5] WHEATER E, SHENKIN S D, MUÑOZ MANIEGA S, *et al*. Birth weight is associated with brain tissue volumes seven decades later but not with MRI markers of brain ageing. Neuroimage Clin, 2021, 31: 102776. doi: 10.1016/j.nicl.2021.102776.
[6] GROVE B J, LIM S J, GALE C R, *et al*. Birth weight and cognitive ability in adulthood: A systematic review and meta-analysis. Intelligence, 2017, 61: 146-158. doi: 10.1016/j.intell.2017.02.001.
[7] CORSI D J, DAVEY SMITH G, SUBRAMANIAN S V. Commentary: challenges to establishing the link between birthweight and cognitive development. Int J Epidemiol, 2013, 42(1): 172-175. doi: 10.1093/ije/dyt022.
[8] SHENKIN S D, DEARY I J, BATTY G D. Commentary: Birthweight and childhood cognition: the use of twin studies. Int J Epidemiol, 2011, 40(4): 1019-1021. doi: 10.1093/ije/dyr100.
[9] PICHET BINETTE A, GAITERI C, WENNSTRÖM M, *et al*. Proteomic changes in Alzheimer's disease associated with progressive Aβ plaque and tau tangle pathologies. Nat Neurosci, 2024, 27(10): 1880-1891. doi: 10.1038/s41593-024-01737-w.
[10] SOLOMON A, MANGIALASCHE F, RICHARD E, *et al*. Advances in the prevention of Alzheimer's disease and dementia. J Intern Med, 2014, 275(3): 229-250. doi: 10.1111/joim.12178.
[11] LANGEH U, SINGH S. Targeting S100B protein as a surrogate biomarker and its role in various neurological disorders. Curr Neuropharmacol, 2021, 19(2): 265-277. doi: 10.2174/1570159X18666200729100427.
[12] SUDLOW C, GALLACHER J, ALLEN N, *et al*. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med, 2015, 12(3): e1001779. doi: 10.1371/journal.pmed.1001779.
[13] COLLINS R. What makes UK Biobank special, Lancet, 2012, 379(9822): 1173-1174. doi: 10.1016/S0140-6736(12)60404-8.
[14] FOSTER H M E, CELIS-MORALES C A, NICHOLl B I, *et al*. The efect of socioeconomic deprivation on the association between an extended measurement of unhealthy lifestyle factors and health outcomes: a prospective analysis of the UK Biobank cohort. Lancet Public Health, 2018, 3(12): e576-e585. doi: 10.1016/S2468-2667(18)30200-7.
[15] CRAIG CL, MARSHALL AL, SJÖSTRÖM M, *et al*. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc, 2003, 35: 1381-1395. doi: 10.1249/01.MSS.0000078924.61453.FB.
[16] SABIA S, FAYOSSE A, DUMURGIER J, *et al*. Association of sleep duration in middle and old age with incidence of dementia. Nat Commun, 2021, 12: 2289. doi: 10.1038/s41467-021-22354-2.
[17] SUN B B, CHIOU J, TRAYLOR M. Plasma proteomic associations with genetics and health in the UK Biobank. Nature, 2023, 622(7982): 329-338. doi: 10.1038/s41586-023-06592-6.
[18] SCHOENFELD D. Partial residuals for the proportional hazards regression model. Biometrika, 1982, 69(1): 239-241. doi: 10.1093/biomet/69.1.239.
[19] Van der WEELE T J, DING P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med, 2017, 167(4): 268-274. doi: 10.7326/M16-2607.
[20] COLE S R, CHU H, GREENLAND S. Multiple-imputation for measurement-error correction. Int J Epidemiol, 2006, 35(4): 1074-1081. doi: 10.1093/ije/dyl097.
[21] TEHRANIFAR P, LIAO Y, FLOM J D, *et al*. Validity of self-reported birth weight by adult women: sociodemographic influences and implications for life-course studies. Am J Epidemiol, 2009, 170(7): 910-917. doi: 10.1093/aje/kwp205.
[22] BENJAMINI Y, HOCHBERG Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Statist Soc B, 1995, 57(1): 289-300. doi: 10.1111/j.2517-6161.1995.tb02031.x.
[23] EMANUEL O M, LEE M, LUTSEY P L, *et al*. Association of birth weight with incident dementia: The Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study. Alzheimer's Dement, 2023, 19(s22): e079218. doi: 10.1002/alz.079218.
[24] ARABZADEH H, DOOSTI-IRANI A, KAMKARI S, *et al*. The maternal factors associated with infant low birth weight: an umbrella review. BMC Pregnancy Childbirth, 2024, 24(1): 316. doi: 10.1186/s12884-024-06487-y.
[25] LIVINGSTON G, HUNTLEY J, LIU K Y, *et al*. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. Lancet, 2024, 404(10452): 572-628. doi: 10.1016/S0140-6736(24)01296-0.
[26] ZANETTI D, TIKKANEN E, GUSTAFSSON S, *et al*. Birthweight, type 2 diabetes mellitus, and cardiovascular disease: addressing the barker hypothesis with mendelian randomization. Circ Genom Precis Med, 2018, 11(6): e002054. doi: 10.1161/CIRCGEN.117.002054.
[27] BACKHOUSE E V, SHENKIN S D, MCINTOSH A M, *et al*. Early life predictors of late life cerebral small vessel disease in four prospective cohort studies. Brain, 2021, 144(12): 3769-3778. doi: 10.1093/brain/awab331.
[28] SCHAAPSMEERDERS P, VAN UDEN IW, TULADHAR A M, *et al*. Ipsilateral hippocampal atrophy is associated with long-term memory dysfunction after ischemic stroke in young adults. Hum Brain Mapp, 2015, 36(7): 2432-2442. doi: 10.1002/hbm.22782.
[29] LU J J, XING X X, QU J, *et al*. Alterations of contralesional hippocampal subfield volumes and relations to cognitive functions in patients with unilateral stroke. Brain Behav, 2024, 14(8): e3645. doi: 10.1002/brb3.3645.
[30] SIMATS A, LIESZ A. Systemic inflammation after stroke: implications for post-stroke comorbidities. EMBO Mol Med, 2022, 14(9): e16269. doi: 10.15252/emmm.202216269.
[31] KIM C, SOHN J H, JANG M U, *et al*. Association between Visit-to-Visit Glucose Variability and Cognitive Function in Aged Type 2 Diabetic Patients: A Cross-Sectional Study. PLoS One, 2015, 10(7): e0132118. doi: 10.1371/journal.pone.0132118.
[32] ZHANG S, WANG A, LIU S, *et al*. Glycemic variability correlates with medial temporal lobe atrophy and decreased cognitive performance in patients with memory deficits. Front Aging Neurosci, 2023, 15: 1156908. doi: 10.3389/fnagi.2023.1156908.
[33] ISIK F I, THOMSON S, CUETO J F, *et al*. A systematic review of the neuroprotective role and biomarker potential of GDF15 in neurodegeneration. Front Immunol, 2024, 15: 1514518. doi: 10.3389/fimmu.2024.1514518.
[34] WEBBER K, PATEL S, KIZER J R, *et al*. Associations of serum GDF-15 levels with physical performance, mobility disability, cognition, cardiovascular disease, and mortality in older adults. medRxiv [Preprint], 2024 Aug 8:2024.08.07.24311629. doi: 10.1101/2024.08.07.24311629.
[35] HUANG Q, TRUMPFF C, MONZEL A S, *et al*. Psychobiological regulation of plasma and saliva GDF15 dynamics in health and mitochondrial diseases. bioRxiv[Preprint], 2024. doi:10.1101/2024.04.19.590241.
[36] WANG D, DAY E A, TOWNSEND L K, *et al*. GDF15: emerging biology and therapeutic applications for obesity and cardiometabolic disease. Nat Rev Endocrinol, 2021, 17(10): 592-607. doi: 10.1038/s41574-021-00529-7.
[37] WANG D, TOWNSEND L K, DESORMEAUX G J, *et al*. GDF15 promotes weight loss by enhancing energy expenditure in muscle. Nature, 2023, 619(7968): 143-150. doi: 10.1038/s41586-023-06249-4.
[38] PENCE B D. Growth differentiation factor-15 in immunity and aging. Front Aging, 2022, 3: 837575. doi: 10.3389/fragi.2022.837575.

[39] ZHANG Y, YANG X, ZHU X L, *et al*. A novel immune-related prognostic biomarker and target associated with malignant progression of glioma. Front Oncol, 2021, 11: 643159. doi: 10.3389/fonc.2021.643159.

[40] ILIOPOULOU L, TZAFERIS C, PRADOS A, *et al*. Different fibroblast subtypes propel spatially defined ileal inflammation through TNFR1 signalling in murine ileitis. Nat Commun, 2025, 16(1): 3023. doi: 10.1038/s41467-025-57570-7.

[41] EIKELENBOOM P, HOOZEMANS J J, VEERHUIS R, *et al*. Whether, when and how chronic inflammation increases the risk of developing late-onset Alzheimer's disease. Alzheimers Res Ther, 2012, 4(3): 15. doi: 10.1186/alzrt118.

[42] WALKER K A, FICEK B N, WESTBROOK R. Understanding the role of systemic inflammation in Alzheimer's disease. ACS Chem Neurosci, 2019, 10(8): 3340-3342. doi: 10.1021/acschemneuro.9b00333.

[43] PARIMISETTY A, DORSEMANS A C, AWADA R, *et al*. Secret talk between adipose tissue and central nervous system via secreted factors-an emerging frontier in the neurodegenerative research. J Neuroinflammation, 2016, 13(1): 67. doi: 10.1186/s12974-016-0530-x.

（2025－03－27收稿，2025－05－16修回）

编辑 汤 洁