Healthcare and Rehabilitation 2 (2026) 100064

Contents lists available at ScienceDirect

Healthcare and Rehabilitation

journal homepage: www.keaipublishing.com/en/journals/hcr/

Full length article

Evidence for the causal relationship between age at first sexual intercourse and multidimensional aging phenotypes from a full life cycle perspective: A mendelian randomization study

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ARTICLE INFO

Keywords:
Age at First Sexual Intercourse
Aging
Causal Inference
Mendelian Randomization

ABSTRACT

Background: The full life cycle perspective emphasizes the profound impact of early-life events on later health. Age at first sexual intercourse (AFS) marks the onset of an individual's sexual development and behavior, which may influence the aging trajectory.
Objective: This study aims to investigate the causal effects of AFS on multidimensional aging phenotypes and identify potential mediating mechanisms from a full life cycle perspective.
Study design: Mendelian Randomization (MR) analysis.
Methods: This study employed two-sample MR analysis, using genetic instruments for AFS to estimate its causal effects on various aging phenotypes, including aging-genetically independent phenotypes (aging-GIP), longevity, frailty index, parental lifespan, healthspan, and self-rated health. Subsequently, a two-step MR mediation analysis was conducted to determine the mediating effects between AFS and aging-GIP.
Results: Earlier AFS was causally associated with lower aging-GIP (β, 0.42; 95%CI, 0.36–0.48). Similar association patterns were observed for longevity (*OR*, 1.41; 95%CI, 1.11–1.78) and parental lifespan (β, 0.33; 95%CI, 0.28–0.39), while negative causal relationships were found with frailty index (β, −0.30; 95%CI, −0.36 to −0.25), healthspan (β, −0.26; 95%CI, −0.33 to −0.18), and self-rated health (β, −0.32; 95%CI, −0.37 to −0.26). Mediation analysis identified 34 exploratory mediators among 145 candidate mediators between AFS and aging-GIP.
Conclusion: The findings underscore the importance of early sexual health education and suggest implementing targeted interventions to mitigate the adverse effects of early sexual behavior on aging. This approach can promote healthy aging and reduce aging disparities caused by early sexual initiation.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AFS, Age at first sexual intercourse; Aging-GIP, Aging-Genetically independent phenotype; CI, Confidence intervals; FDR, False discovery rate; GWAS, Genome-wide association study; IVs, Instrumental variables; IVW, Inverse-variance weighted; LDSC, Linkage disequilibrium score; LOO, Leave-one-out; MR, Mendelian randomization; MVMR, Multivariable Mendelian randomization; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; OR, Odds ratio; RCT, Randomized controlled trial; SNPs, Single-nucleotide polymorphisms; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; UVMR, Univariable Mendelian randomization

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https://doi.org/10.1016/j.hcr.2026.100064
Received 24 November 2025; Received in revised form 29 January 2026; Accepted 25 February 2026

1. Introduction

The full life cycle perspective highlights the impact of early-life events on later health and diseases from birth to aging. This framework provides a critical theoretical basis for understanding the complex mechanisms of health and aging. From this perspective, age at first sexual intercourse (AFS) is a key early-life event whose effects may be lifelong, triggering a series of chain reactions. Previous studies have shown that early sexual initiation is associated with a higher risk of sexually transmitted infections,[1] a greater likelihood of multiple sexual partnerships,[2] adverse sexual and reproductive health outcomes,[3] and a range of later-life health conditions.[4–6] AFS not only signifies the start of an individual's sexual development but may also exert a profound influence on the aging process through multiple pathways. Aging, as the terminal event of the life course, encompasses physiological function decline, chronic disease accumulation, and changes in health status. However, whether AFS has a causal impact on aging remains unclear.

Some interrelated biological pathways may link earlier AFS to accelerated aging. First, earlier puberty, which is a predictor of earlier AFS, is associated with prolonged exposure to sex hormones,[7] which increases oxidative stress and DNA damage.[8] Second, an unintended pregnancy associated with early sexual initiation may lead to chronic psychological stress,[9] which has been linked to accelerated aging.[10] Moreover, AFS could be a primary exposure for two reasons. First, it is a behavioral trait that can be influenced by sexual health education interventions, making it an actionable target for promoting healthy aging. Second, while previous studies have linked AFS to psychiatric disorders,[11] cardiovascular diseases,[12] and cancers,[6] its long-term causal effect on multidimensional aging remains unclear. Filling this gap is critical for advancing life-course epidemiology and public health practice.

The long time span between AFS and aging raises an urgent question: how AFS may exert indirect long-term effects on late-life aging through multiple pathways in the complex life trajectory. Convincing evidence suggested that AFS was associated with a variety of preventable or modifiable lifestyles, behaviors, and diseases,[3,12–14] that could potentially impact the aging process.[15–18] These effects are unlikely to be a simple on-off mechanism; instead, they require tracing the entire life course from early to late life and examining the multiple influencing factors and mediating effects involved. Therefore, systematically studying the potential mediating pathways between AFS and aging from a full life cycle perspective can help design targeted life-course intervention strategies for individuals with earlier sexual experiences, compensate for the loss of early health capital, and narrow the gap in aging risks between these individuals and those with health advantages.

However, prospective cohort studies examining the association and mediating factors between AFS and aging require long-term follow-up and are susceptible to reverse causation and confounding. Conducting a randomized controlled trial (RCT) is neither feasible nor ethical. Fortunately, Mendelian randomization (MR) is an effective alternative method that uses genetic variations as instrumental variables (IVs) to infer potential causal relationships between exposures and outcomes,[19] effectively addressing the limitations of cohort studies and RCTs. Multivariable MR (MVMR) extends traditional MR, enabling equivalent mediation analysis within a two-step MR framework by conditionally estimating associations of potential pleiotropic traits or mediators.[20]

Therefore, in this two-step, two-sample MR study, we aimed to (i) estimate the causal effects of AFS on a panel of aging phenotypes spanning aging-genetically independent phenotypes (aging-GIP), including frailty index, parental lifespan, longevity, healthspan, and self-rated health, and (ii) map potential life-course pathways by screening putative mediators across lifestyles, behaviors, emotions, physiological characteristics, and diseases. In this work, we focus on multidimensional aging as captured by aging-GIP, a composite phenotype that summarizes shared genetic liability across lifespan- and health-related traits, thus reflecting a broad profile of functional and clinical aging rather than a single aging clock. We hypothesized that genetically predicted earlier AFS would be causally associated with lower aging-GIP, including shorter longevity and parental lifespan, and a higher frailty index, consistent with the full life course framework. Given the complex and potentially context-dependent nature of healthspan and self-rated health, findings for these two outcomes were interpreted as exploratory. The findings can enhance understanding of the consequences and uncover underlying possible mechanisms of sexual initiation timing on aging, and inform preventive strategies—ultimately improving targeted healthcare and lifestyle interventions by shedding light on key aging-related factors.

2. Methods

2.1. Study design

We used the summary-level genome-wide association study (GWAS) data, which is publicly available; thus, this study did not require ethical review. Ethical approvals for the original GWAS datasets are detailed in their respective publications cited herein. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)-MR guidelines (Supplementary Checklist).[21] The MR study had two analysis phases (Fig. 1). Initially, we applied univariable MR (UVMR) analysis using single nucleotide polymorphisms (SNPs) as genetic IVs to proxy exposure and assess the causal association between AFS and six aging phenotypes. We then screened 145 candidate mediators, including 34 lifestyle factors, 26 behaviors and emotions, 23 physiological manifestations, and 62 diseases for causal associations between AFS and aging-GIP, and quantified the mediation effects of each mediator using two-step MR.

2.2. Data sources for exposures, mediators, and outcomes

2.2.1. Exposures

Aggregate statistical data on AFS were obtained from the largest GWAS meta-analysis to date, [5] which included 397,338 individuals (182,791 males, 214,547 females) from the UK Biobank. AFS was treated as a continuous variable and assessed via the question: "What was your age when you first had sexual intercourse?"

2.2.2. Mediators

We selected 145 putative mediators based on four strict criteria (Supplementary Method 1), and spanned four domains: lifestyle factors (e.g., diet-related traits), behaviors, and emotional traits (negative emotions), physiological manifestations (e.g., frailty index), and diseases (e.g., specific cardiovascular diseases). We applied four prespecified screening criteria to identify mediators suitable for two-step MR: (1) AFS should be causally associated with the mediator, but not vice versa. (2) Mediators should be causally associated with aging-GIP. (3) Mediators should have a direct causal effect on aging-GIP independently of AFS. (4) The association of AFS with mediators and the association of mediators with aging-GIP should be in the same direction. Finally, 34 exploratory mediators were included in the mediation analysis for aging-GIP.

Key mediators were prioritized for their role as sequential nodes in the life-course chain connecting early sexual initiation to late-life aging: (1) attention-deficit/hyperactivity disorder (ADHD) and emotional traits reflect early-life neurobehavioral characteristics that are both effects of earlier AFS and direct risk factors for aging-related adverse outcomes[22,23]; (2) Specific cardiovascular diseases represent mid-life chronic conditions that mediate the long-term impact of early-life behaviors on aging[12,24]; (3) Frailty index is a late-life clinical marker of aging that integrates cumulative deficits from earlier AFS, serving as a critical downstream mediator linking AFS-related trajectories to

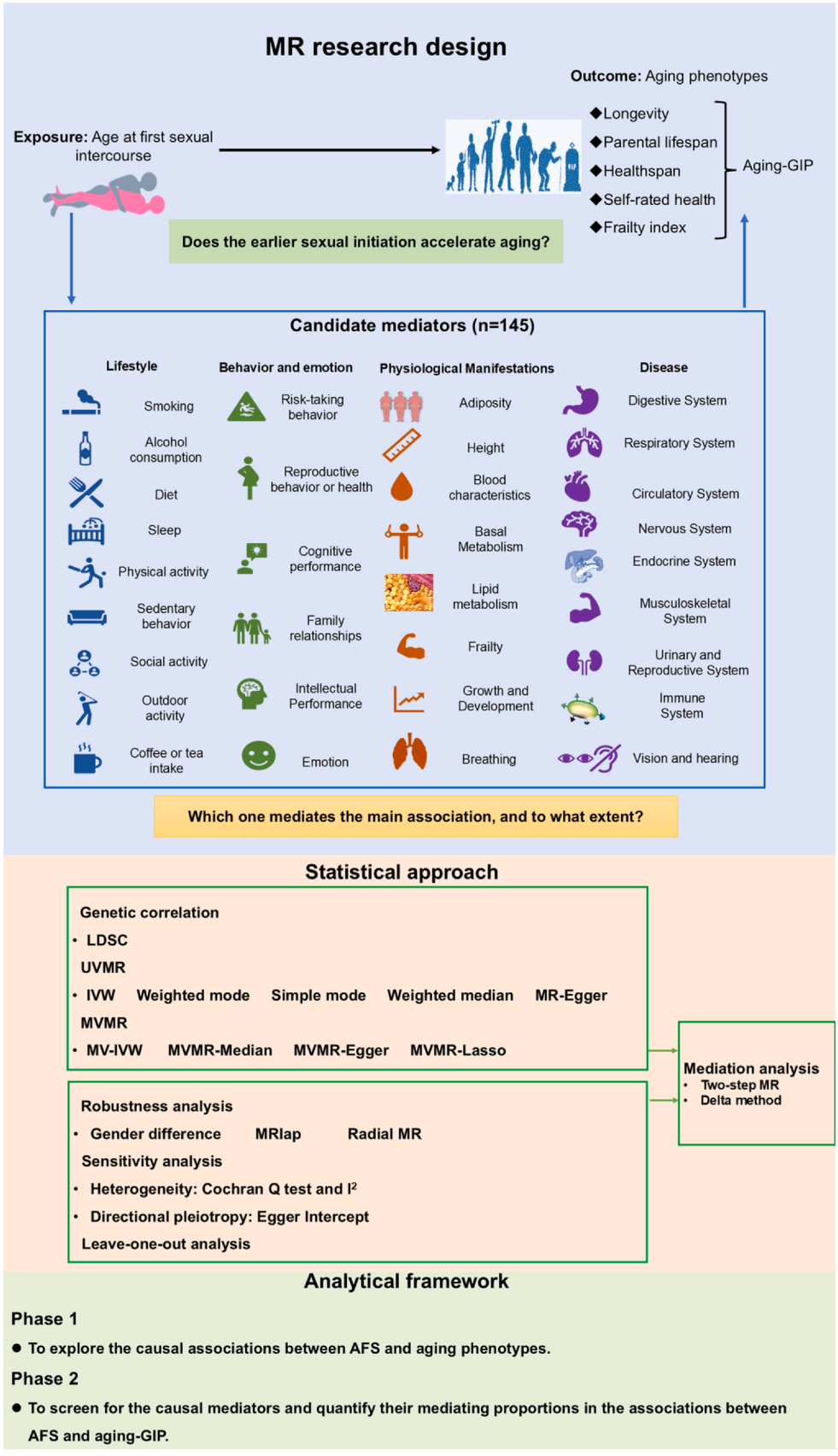

Fig. 1. Overview of the study design. Note: This MR study comprised two analysis phases. In phase 1, we explored the causal associations between AFS and aging phenotypes. In phase 2, we screened for the causal mediators and quantified their mediating proportions in the associations between AFS and aging-GIP. Abbreviations: MR, mendelian randomization; AFS, age at first sexual intercourse; Aging-GIP, aging-genetically independent phenotype; LDSC, linkage disequilibrium score; UVMR, univariable mendelian randomization; IVW, inverse-variance weighted; MVMR, multivariate mendelian randomization; MV-IVW, multivariate inverse-variance weighted.

functional decline in old age.[25] This selection ensures the mediation pathways align with the full life-cycle theory, capturing key developmental transitions from early life to late aging.

2.2.3. Outcomes

This study included aging-GIP, longevity, frailty index, parental lifespan, healthspan, and self-rated health as outcomes to

comprehensively capture multidimensional aging. Summary-level GWAS meta-analysis data for aging-GIP were derived from 154,478 participants of European descent.[26] Aging-GIP is a composite genomic factor derived from the five aforementioned aging-related traits and can be interpreted as a summary measure of overall healthy aging propensity. Longevity data were obtained from a meta-analysis where European ancestry participants were defined as a binary phenotype: cases were individuals who lived ≥ 90th percentile (n = 11,262), and controls (n = 25,483) were individuals whose age at death or last follow-up was ≤ 60th percentile.[27] Summary statistics for the frailty index were extracted from a GWAS meta-analysis of the UK Biobank and Swedish Twin-Gene datasets, including 175,226 participants of European ancestry.[28] The parental lifespan GWAS comprised unrelated European ancestry individuals reporting 512,047 maternal and 500,193 paternal lifespans.[29] GWAS data for healthspan (n = 300,447) and self-rated health (n = 111,749) were sourced from the UK Biobank.[30,31] Detailed information on the GWAS data for each outcome is provided in Supplementary Method 2.

2.3. Statistical analysis

2.3.1. Linkage disequilibrium score (LDSC) regressive analysis

Previous studies suggest that if a causal relationship exists between two traits and both have non-zero heritability, a genetic correlation should be present.[32] We therefore used LDSC regression to calculate the genetic correlation between AFS and aging phenotypes. LDSC regression was performed using GWAS summary data to estimate the regression slope.[33] European ancestry data from the 1000 Genomes Project served as the linkage disequilibrium reference panel, consistent with the European origin of the GWAS samples.[34]

2.3.2. UVMR and MVMR analysis

We applied UVMR to assess the causal effect of AFS and each mediator on aging phenotypes. MVMR was used to estimate the direct effect of each mediator on aging phenotypes after adjusting for AFS, determining whether each mediator exerted a causal effect on aging phenotypes independent of AFS.

All MR analyses adhered to three core assumptions.[19] First, genetic variants must be strongly associated with the UVMR exposure and at least one of the MVMR multiple exposures. Second, genetic variants must not be associated with confounders of the relationships between each exposure's instruments and each outcome. Third, genetic variants must affect each outcome solely through the respective exposure. In UVMR, the inverse-variance weighted (IVW) method was used to estimate effect sizes. A random-effects IVW model was applied if heterogeneity was detected; otherwise, a fixed-effects IVW model was used.[35] In MVMR, the MV-IVW method was employed as the primary analytical approach.[36] Given that the IVW method satisfied MR assumptions, it produced the most precise, unbiased, and efficient causal estimates.[37] Details of other UVMR and MVMR methods are provided in Supplementary Method 3.

2.3.3. Mediation MR analysis

A two-step MR approach was used to evaluate whether specific factors mediated the relationship between AFS and aging phenotypes.[20] The first step involved using UVMR to estimate the causal effect ($\beta 1$) of AFS on each mediator. Reverse MR was conducted between each mediator and AFS to detect potential bidirectionality that might compromise the validity of the mediation model. The second step estimated the causal effect ($\beta 2$) of each mediator on aging phenotypes using MVMR adjusted for AFS, provided the mediator was causally associated with the aging phenotype in UVMR. The mediation proportion of each mediator in the association between AFS and aging phenotypes was calculated as ($\beta 1 \times \beta 2$) divided by the total effect. The delta method was used to compute the 95% confidence intervals (CIs) for the mediation proportions.[38] A single mediation proportion exceeding 100% was truncated at 100%, as this represents the maximum threshold for meaningful mediation. Intuitively, a mediation proportion of 30% indicates that approximately one-third of the total AFS → outcome association is statistically consistent with transmission through the AFS → mediator and mediator → outcome paths. Because mediators were evaluated one at a time, these proportions were interpreted as non-additive and were not intended to sum to 100% across mediators.

In practice, a single joint multivariable model with numerous potentially correlated mediators is often infeasible with summary-level data due to multicollinearity and limited instrument overlap across mediators. Therefore, we used a prespecified screening strategy and evaluated mediators in a single-mediator framework, prioritizing interpretability over attributing independent contributions.

2.3.4. Selection of genetic instruments

On UVMR of AFS and aging phenotypes, genetic instruments for AFS were screened through multiple steps to ensure analytical reliability. First, SNPs were selected at a genome-wide significance level ($P < 5 \times 10^{-8}$) and were independent of each other (LD $R^2 < 0.001$ within 10,000 KB). Second, IVs associated with aging phenotypes but not AFS (identified by $P < 5 \times 10^{-8}$ in outcome datasets) were excluded. Third, *F*-statistics were calculated for each instrumental variable, retaining only those with $F > 10$ to avoid weak instrument bias.[39] *F*-statistics was calculated by $F = [R^2 \times (N - 2)]/1 - R^2$, where $R^2 = \beta^2/(\beta^2 + SE^2 \times N)$. N represents the number of participants, and β is the estimated effect of the SNP on the outcome.[40] Fourth, palindromic and incompatible SNPs were removed after harmonizing exposure and outcome data. Fifth, MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) analysis was performed to eliminate outlier pleiotropic SNPs ($P < 0.05$, Nb-Distribution = 1000). Finally, the MR Steiger test was conducted to remove IVs that could lead to reverse causal inferences.[41]

In two-step MR analysis, genetic instruments for each mediator and AFS were genome-wide significant ($P < 5 \times 10^{-8}$) and independent (LD $R^2 < 0.001$ within 10,000 KB). On MVMR analysis, genetic instruments consisted of SNPs that were genome-wide significant ($P < 5 \times 10^{-8}$) in either the AFS GWAS or each mediator GWAS and were independent (LD $R^2 < 0.001$ within 10,000 KB).

2.3.5. Robustness analysis

Given that the genetic overlap of AFS between genders is 0.79,[5] indicating partial gender specificity, we investigated the potential effects of AFS on aging phenotypes by gender on UVMR. Additionally, we conducted Radial MR-IVW and Radial MR-Egger analysis using improved second-order weights to identify outliers and repeated the previous UVMR analysis of AFS and six aging phenotypes.[42] Finally, multiple approaches were used to assess the potential impact of bias from partial sample overlap between AFS, mediator phenotypes, and aging phenotypes: (i) an online calculator was used to evaluate bias and type I error rates associated with sample overlap (https://sb452.shinyapps.io/overlap/),[43] and (ii) the MRlap method was employed to mitigate biases from sample overlap, winner's curse, and weak instruments.[44]

2.3.6. MR sensitivity analysis

MR-Egger regression based on the intercept term was performed to detect directional pleiotropy in MR results.[45] Heterogeneity was examined using the Cochran Q test and I^2 index, with $P < 0.05$ and $I^2 > 25\%$ indicating significant heterogeneity.[46] Leave-one-out (LOO) analysis was conducted to evaluate the influence of individual SNPs on the observed results.

To improve readability, we aligned key sensitivity checks with the specific threats they address: (i) weak-instrument bias was minimized using genome-wide significant variants and *F*-statistics > 10; (ii) heterogeneity and influential outliers were assessed using Cochran's Q/I^2, Radial MR, and MR-PRESSO analyses; (iii) pleiotropy was evaluated using the MR-Egger intercept and MR-PRESSO; (iv) directionality was

assessed using Steiger filtering and reverse MR where relevant; and (v) potential bias from sample overlap and winner's curse was quantified using an overlap calculator and corrected using MRlap. Primary conclusions were based on IVW/MV-IVW estimates that were directionally consistent with at least one pleiotropy-robust estimator and showed no evidence of directional pleiotropy.

All MR analyses were performed using R packages TwoSampleMR, MVMR, MRPRESSO, RadialMR, MendelianRandomization, corrr, and MRlap in R software (version 4.3.0, University of Auckland, Auckland, New Zealand; R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided, with $P < 0.05$ indicating statistical significance. In analyzing causal associations between AFS and six aging phenotypes, false discovery rate (FDR) Q values were calculated using the Benjamini–Hochberg method to address multiple hypothesis testing.[47] MR estimates are presented as odds ratios (ORs), β coefficients, or proportions with corresponding 95% CI.

Table 1
Overview of the GWAS data used in the study.

Phenotype	Unit	Sample size (case/control)	Ancestry	Consortium or cohort study	Year of publication	PubMed ID
Exposure						
Age at first sexual intercourse	Year	397,338	European	UK Biobank	2021	34211149
Age at first sexual intercourse for males	Year	182,791	European	UK Biobank	2021	34211149
Age at first sexual intercourse for females	Year	214,547	European	UK Biobank	2021	34211149
Outcome						
aging-GIP	SD	154,478	European	Meta	2022	37118362
Longevity	Event	11,262/ 25,483	European	Meta	2019	31413261
Frailty index	SD	175,226	European	UK Biobank, TwinGene	2021	34431594
Parental lifespan	Year	1012,240	European	UK Biobank, LifeGen	2019	30642433
Healthspan	Log-transformed hazard ratio	300,447	European	UK Biobank	2019	30729179
Self-rated health	1-point in the score	111,749	European	UK Biobank	2017	27864402
Qualified mediators n = 34						
Lifestyle n = 7						
Overall healthy diet	SD	258,758	European	UK Biobank	2022	35653391
Eat eggs, dairy, wheat, sugar	Event	355,835/ 105,211	European	UK Biobank	2018	29846171
Sleep disorders	Event	19,155/ 197,545	European	FinnGen	2021	29846171
Sleep duration	SD	335,410	European	UK Biobank	2017	29846171
Social activities: Adult education class	Event	33,398/ 427,971	European	UK Biobank	2018	29846171
Ground coffee consumption	SD	72,276	European	UK Biobank	2022	35653391
Instant coffee consumption	SD	180,764	European	UK Biobank	2022	35653391
Behavior and Emotion n = 6						
Breastfed as a baby	Event	251,150/ 100,944	European	UK Biobank	2018	29846171
Miserableness	Event	195,435/ 259,547	European	UK Biobank	2018	29846171
Irritability	Event	125,001/ 317,168	European	UK Biobank	2018	29846171
Guilty feelings	Event	129,383/ 321,321	European	UK Biobank	2018	29846171
Sensitivity / hurt feelings	Event	249,799/ 199,620	European	UK Biobank	2018	29846171
Tense / highly strung	Event	78,408/ 369,553	European	UK Biobank	2018	29846171
Physiological Manifestations n = 6						
Childhood BMI	SD	39,620	European	GIANT	2020	33045005
WHR	SD	212,244	European	GIANT	2015	25673412
Eosinophil percentage	SD	349,861	European	UK Biobank	2018	29846171
WBC count	SD	563,946	European	BCC	2020	29846171
Frailty index	SD	175,226	European	UK Biobank, TwinGene	2021	34431594
Hand grip strength (right)	SD	461,089	European	UK Biobank	2018	29846171
Diseases n = 15						
Barrett's esophagus	Event	13,358/ 43,071	European	UK Biobank, 23andMe	2021	34187846
Pulmonary embolism	Event	4185/ 214,228	European	FinnGen	2021	29846171
COPD	Event	13,530/ 454,945	European	Meta	2021	34594039
CHD	Event	22,233/ 64,762	European	CARDIoGRAM	2011	21378990
MI	Event	20,917/ 440,906	European	Meta	2021	34594039
Hypertension	Event	42,857/ 175,935	European	FinnGen	2021	29846171
Peripheral atherosclerosis	Event	6631/ 162,201	European	FinnGen	2021	29846171
Coronary atherosclerosis	Event	23,363/ 187,840	European	FinnGen	2021	29846171
Venous thromboembolism	Event	9176/ 209,616	European	FinnGen	2021	29846171
IHD	Event	30,952/ 187,840	European	FinnGen	2021	29846171
Neuroticism	Event	393,411	European	Meta	2018	29892013
ADHD	Event	20,183/ 35,191	European	PGC	2017	30478444
Type 1 diabetes	Event	6447/ 451,248	European	Meta	2021	34594039
Hypothyroidism	Event	7183/ 59,893	European	FinnGen	2021	29846171
Atopic dermatitis	Event	22,474/ 774,187	European	Meta	2021	34454985

Note: Only qualified mediators are shown in Table 1. See Supplementary Table 1 for information on all 145 candidate mediators

Abbreviations: ADHD, attention deficit hyperactive disorder; aging-GIP, aging-genetically independent phenotype; BCC, Blood Cell Consortium; BMI, body Mass Index; CARDIoGRAM, Coronary Artery Disease Genome Wide Replication and Meta-analysis; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; GIANT, Genetic Investigation of Anthropometric Traits; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use; GWAS genome-wide association study; IHD, ischemic heart diseases; MI, myocardial infarction; PGC, Psychiatric Genomic Consortium; SD, standard deviation; WBC count, white blood cell count; WHR, waist-to-hip ratio

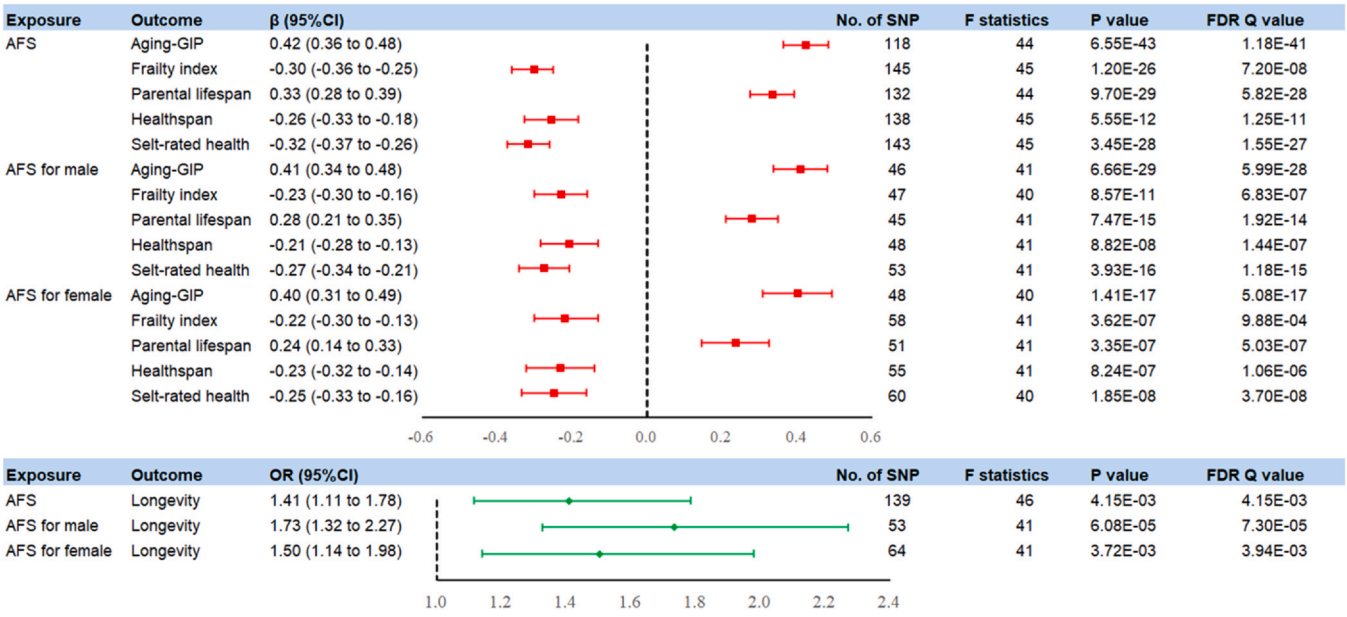

Fig. 2. UVMR estimates for the causal associations between AFS and aging phenotypes. Note: MR estimates were derived from the IVW method in UVMR. All the significant causal associations persisted with false discovery rate adjustment for multiple comparisons. The dots represent β coefficients or ORs, and the error bars represent 95% CIs. All statistical tests were two-sided. $P < 0.05$ was considered significant. Abbreviations: aging-GIP, aging-genetically independent phenotype; AFS, age at first sexual intercourse; CI, confidence interval; FDR, false discovery rate; IVW, inverse-variance weighted; OR, odds ratio; SNP, single nucleotide polymorphism; UVMR, univariable mendelian randomization.

3. Results

3.1. Basic characteristics of the MR study

Table 1 summarizes the GWAS datasets for AFS, 34 qualified mediators, and six aging phenotypes. Supplementary Table 1 lists all 145 candidate mediators, selected based on a comprehensive literature review (Supplementary Table 2). Because aging-GIP is constructed from GWAS signals shared across several aging-related traits, we examined the related component outcomes (longevity, frailty index, parental lifespan, healthspan, and self-rated health) to provide trait-specific interpretation alongside the composite aging-GIP metric.

3.2. Causal effects of AFS on aging phenotypes

LDSC regression revealed genetic correlations between AFS and aging-GIP, longevity, frailty index, parental lifespan, healthspan, and self-rated health (absolute value range of r_g: 0.23–0.53; Supplementary Table 3). After rigorous IV screening, the number of AFS-related SNPs used for each aging phenotype ranged from 118 to 145. All *F*-statistics for these SNPs exceeded 10 (Fig. 2), indicating no weak instrument bias.

In UVMR, genetically determined AFS showed positive causal relationships with aging-GIP (IVW-estimated β, 0.42; 95%CI, 0.36–0.48), longevity (*OR*, 1.41; 95%CI, 1.11–1.78), and parental lifespan (β, 0.33 years; 95%CI, 0.28–0.39). In contrast, AFS had negative causal relationships with frailty index (β, −0.30; 95%CI, −0.36 to −0.25), healthspan (β, −0.26; 95%CI, −0.33 to −0.18), and self-rated health (β, −0.32 points; 95%CI, −0.37 to −0.26) after FDR adjustment for multiple comparisons (Fig. 2). All UVMR estimates were validated by at least one other MR analysis method (Supplementary Table 4). Although some MR-Egger results showed no association ($P > 0.05$), their estimated values were consistent in direction with IVW results. Some IVs were heterogeneous, but instrumental validity tests confirmed sufficient instrument strength (all *F*-statistics ≥ 40), and no directional pleiotropy was observed (*P* for Egger intercept > 0.05) (Supplementary Table 5). Scatter plots were generated to visualize these relationships (Supplementary Figure 1). LOO analyses demonstrated that no single SNP substantially influenced the causal associations (Supplementary Figure 2).

3.3. Robustness analyses of the causal relationship between AFS and aging phenotypes

In gender-stratified analyses, effect directions were consistent across males and females for all six aging outcomes (Fig. 2). While point estimates differed modestly by sex for some outcomes, CIs largely overlapped, suggesting broadly comparable genetic effects. We therefore interpreted the absence of strong sex heterogeneity as supporting the overall conclusions, while noting that pleiotropy indicators were more evident in men (AFS→self-rated health) than in women (AFS→healthspan) (Supplementary Table 5), consistent with the cautious interpretation of these two outcomes.

Radial MR-IVW and MR-Egger analysis using improved second-order weights identified outliers (Supplementary Table 7),[42] and repeated UVMR analysis, excluding these outliers, confirmed the persistence of the causal relationship between AFS and aging phenotypes with no gender differences (Supplementary Table 6). Galbraith radial plots were used to visualize these outliers (Supplementary Figure 3), being better than traditional scatter plots by eliminating the need for genetic data recoding and enabling more direct detection of outliers and influential data points.[42]

The type 1 error rate due to sample overlap between AFS and aging phenotypes was controlled below 0.05 (Supplementary Table 8). We additionally reported both uncorrected and MRlap-corrected estimates (Supplementary Table 9). Notably, MRlap corrections were small for several exposure–outcome pairs, which is plausible when genetic instruments are strong and overlap-induced bias is limited relative to sampling variability; nonetheless, we interpreted these findings cautiously given the heavy reliance on UK Biobank data.

3.4. Mediation effect analysis

3.4.1. Effect of AFS on mediators

After mediator selection, 34 of the 145 candidates met all screening criteria and were included as mediators for aging-GIP (Fig. 3). Fig. 4

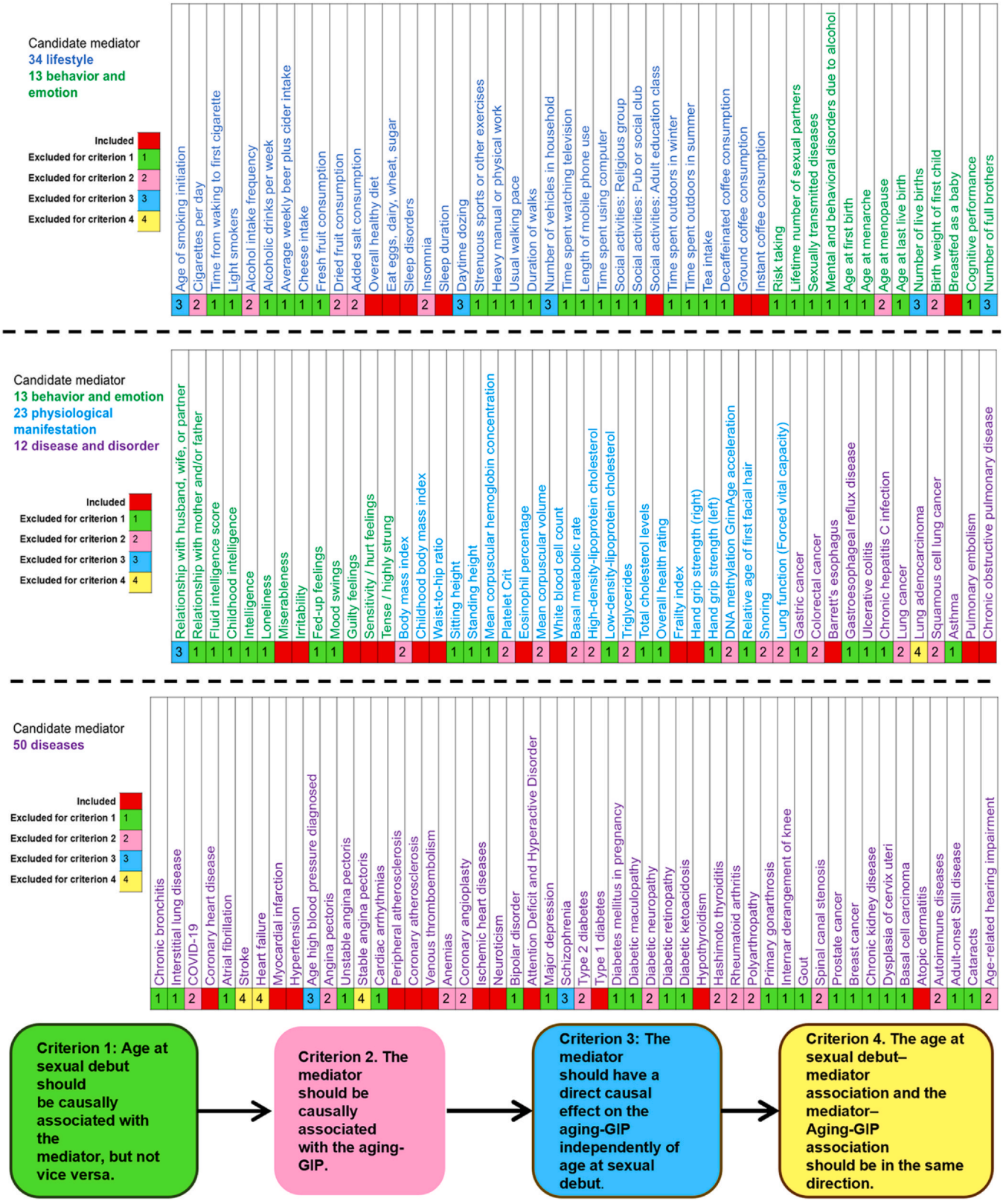

Fig. 3. Selection process for mediators of the causal associations of AFS with aging-GIP.

presents the IVW-estimated effect sizes of genetically determined AFS on each of the 34 mediators, including 7 lifestyle factors, 6 behaviors and emotions, 6 physiological manifestations, and 15 diseases. Reverse MR analyses showed causal effects of ADHD on AFS, but the result was likely driven by directional pleiotropy (all $P < 0.05$). Heterogeneity was observed among IVs for other mediators, but no directional pleiotropy was detected in the causal associations between AFS and these mediators (Supplementary Tables 10 and 11).

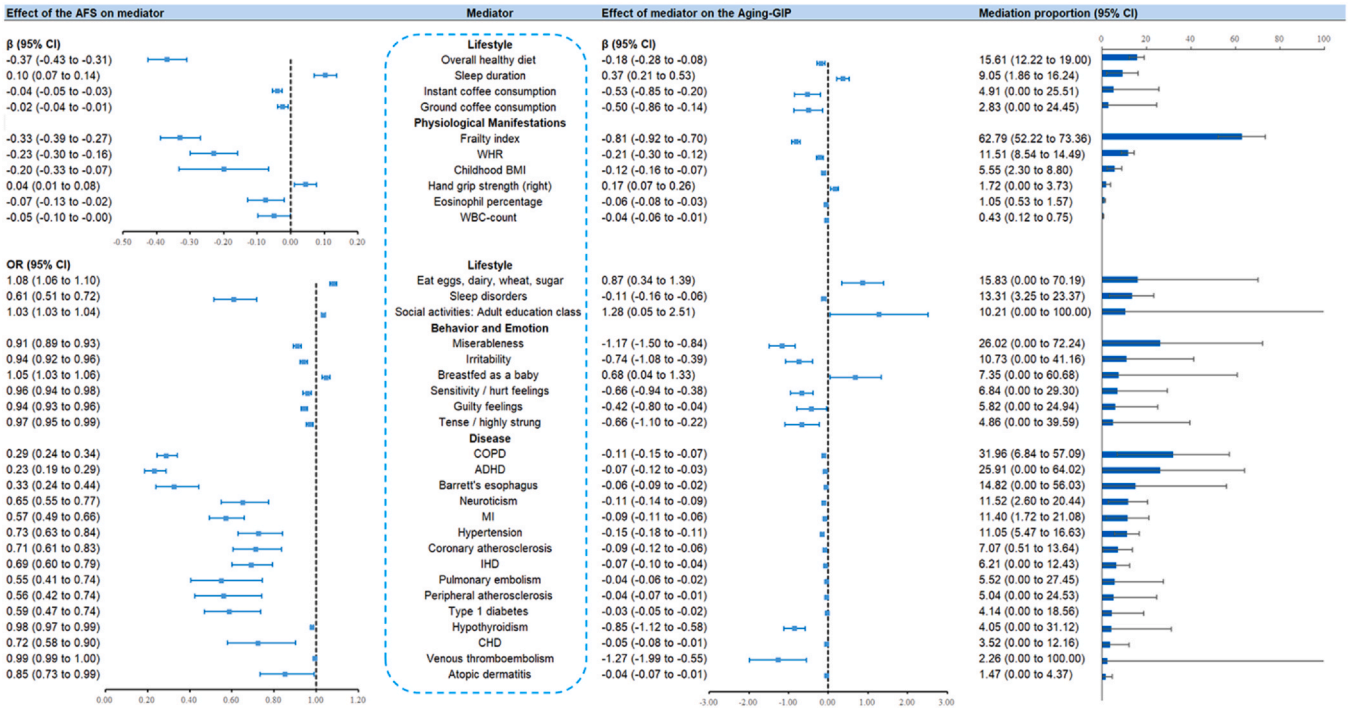

Fig. 4. Mediating role of each mediator in the causal associations of AFS with aging-GIP. Left: UVMR estimates for the causal effect of AFS on each mediator. Middle: MVMR estimates for the causal effect of each mediator on aging-GIP adjusted for AFS. Right: the mediation proportion of each mediator in the causal association between AFS and aging-GIP. Note: Mendelian randomization (MR) estimates were derived from the inverse-variance weighted (IVW) method in UVMR (univariate MR) and the MV-IVW (multivariate IVW) method in MVMR (multivariate MR). The data are presented as odds ratios (ORs), β coefficients, or proportions, with corresponding 95% confidence intervals (CIs). The dots represent *ORs* or β coefficients, and the bars represent proportions, with the error bars indicating 95% CIs. All statistical tests were two-sided. $P < 0.05$ was considered significant. Abbreviations: aging-GIP, aging-genetically independent phenotype; AFS, age at first sexual intercourse; ADHD, attention deficit hyperactive disorder; BMI, body Mass Index; CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart diseases; MI, myocardial infarction; OR, odds ratio; WBC count, white blood cell count; WHR, waist-to-hip ratio.

3.4.2. *Effect of each mediator on Aging-GIP*

UVMR and MVMR estimates for the associations between the 34 qualified mediators and aging-GIP are provided in Supplementary Tables 12 and 13. In MVMR adjusted for AFS, consuming eggs, dairy, wheat, or sugar (MV-IVW-estimated β, 0.87; 95%CI, 0.34–1.39), attending adult education classes during leisure (1.28; 0.05–2.51), being breastfed in infancy (0.68; 0.04–1.33), and each standard deviation (SD) increase in sleep duration (0.37; 0.21–0.53) or right hand grip strength (0.17; 0.07–0.26) were associated with higher aging-GIP. In contrast, genetically determined unhealthy lifestyles, behaviors, and emotions, and physiological manifestations were associated with lower aging-GIP, with β values ranging from −1.17 (-1.50 to −0.84) for miserableness to −0.04 (-0.06 to −0.01) for each SD increase in white blood cell count. Similar causal associations with aging-GIP were observed for 15 diseases, including Barrett's esophagus, pulmonary embolism, chronic obstructive pulmonary disease (COPD), coronary heart disease, myocardial infarction (MI), hypertension, peripheral atherosclerosis, coronary atherosclerosis, venous thromboembolism, ischemic heart disease, neuroticism, ADHD, type 1 diabetes, hypothyroidism, and atopic dermatitis. Each disease was associated with a 0.03–1.27 SD reduction in aging-GIP after adjusting for AFS (Fig. 4).

3.4.3. *Mediation effect of each mediator*

Among lifestyle, behavior and emotion, and physiological manifestations, the frailty index (mediation proportion, 62.79%) and miserableness (26.02%) each mediated more than 20% of the total effect of AFS on aging-GIP. The other 17 mediators each mediated 0.43–15.83% of the total effect. For diseases, the top three mediators were COPD (31.96%), ADHD (25.91%), and Barrett's esophagus (14.82%), with the remaining 12 diseases mediating 1.47–11.52% of the total effect (Fig. 4).

All MV-IVW estimates were supported by at least one sensitivity analysis (Supplementary Table 13). The type 1 error rate due to sample overlap between certain mediators and aging phenotypes was below 0.05 (Supplementary Table 8), and causal associations were validated by the MRlap method (Supplementary Table 9).

4. Discussion

Adopting a full life cycle perspective, this study systematically explored the causal impact of AFS on multidimensional aging phenotypes and its potential mediating mechanisms. The full life cycle concept emphasizes the profound influence of early-life events on later health and aging, and AFS may exert lifelong effects as a key early-life event. We found that genetically determined earlier AFS was associated with lower aging-GIP, parental lifespan, and longevity, and a higher frailty index, healthspan, and self-rated health. We further identified 34 exploratory causal mediators of 145 common lifestyles, behaviors and emotions, physiological functions, and diseases in the pathways from AFS to aging-GIP spanning multiple life stages from prenatal to old age. Genetically determined miserableness, frailty index, COPD, and ADHD each mediated more than 20% of the total effect of AFS on aging-GIP.

MR results indicated that earlier sexual debut was causally associated with multiple aging phenotypes, leading to shorter aging-GIP, increased frailty, reduced longevity, and shorter parental lifespan, consistent with some previous studies.[25,48] This may be attributed to elevated risks of unintended pregnancies, sexually transmitted diseases, substance abuse, and physical health conditions during adolescence and adulthood, which are closely linked to earlier sexual intercourse,[1,4,49] and can significantly compromise life expectancy and elevate aging-related vulnerabilities. Thus, our findings provide compelling evidence for prioritizing early sexual health education, as delaying sexual

initiation and fostering healthy sexual attitudes emerge as effective strategies to promote healthy aging.

In this study, aging-GIP, a comprehensive aging phenotype that partially overlaps with healthspan and self-rated health, may obscure trait-specific patterns, necessitating separate analyses of its constituent outcomes. Overall, the direction and magnitude of associations for aging-GIP, frailty index, longevity, and parental lifespan were broadly consistent across sensitivity analyses; we therefore consider these findings robust and aligned with the full life cycle hypothesis. In contrast, the apparent favorable associations between earlier AFS and healthspan/self-rated health were counterintuitive and should be interpreted as exploratory. Several factors may explain this pattern. First, horizontal pleiotropy is a likely contributor: genetic IVs may influence AFS, healthspan. and self-rated health directly through independent biological or behavioral pathways.[50] AFS is shaped by extremely complex factors, including social environment, education, personality, and psychological state, making it nearly impossible to identify SNPs that exclusively affect AFS without impacting other health-related behaviors. Second, methods for detecting pleiotropy are imperfect; approaches such as MR-Egger and MR-PRESSO only detect directional pleiotropy.[45] Third, MR typically assumes a linear causal relationship,[19] and non-linear effects of AFS on healthspan and self-rated health would lead to incorrect conclusions from linear MR analyses. Accordingly, these two outcomes are interpreted with caution and do not alter the overarching conclusion that earlier AFS is potentially detrimental to multidimensional aging.

To elucidate the complex mechanisms underlying these causal associations, we further characterized the multifaceted mediators linking sexual initiation to aging-GIP. We identified 34 exploratory mediators between AFS and aging-GIP, with the frailty index, miserableness, COPD, and ADHD each accounting for more than 20% of the total mediation effect. The frailty index emerged as the dominant mediator ($> 60\%$) in the AFS–aging-GIP association. This may partly reflect conceptual overlap: aging-GIP is a composite construct capturing shared genetic liability across multiple aging-related traits, while frailty represents a multidimensional summary of accumulated health deficits. Thus, the high mediation proportion should be interpreted as frailty capturing a major component of multidimensional aging rather than an independent or additive pathway. Miserableness is a plausible mediator because earlier sexual debut appears to increase susceptibility to depressive phenotypes, and sustained depressive/negative-affect states can accelerate aging through biological and functional pathways: MR evidence links earlier AFS to a higher risk of major depressive disorder,[51] and depression/negative affect has been associated with accelerated biological aging.[52] Additionally, longitudinal data show that depressive symptoms predict subsequent frailty and its components, consistent with the strong weighting of aging-GIP toward overall health decline.[53] COPD may mediate the AFS–aging-GIP association because earlier sexual debut often co-occurs with long-term risk-exposure trajectories, especially smoking-related patterns, and COPD is increasingly recognized as an accelerated lung-aging condition characterized by cellular senescence and chronic inflammation that can spill over into multisystem dysfunction and functional decline; consistent with this, frailty is common in COPD and linked to worse outcomes, aligning closely with the health-deficit domains captured by aging-GIP.[54,55] ADHD may also act as a mediator because an impulsivity-prone developmental profile is associated with earlier AFS, while ADHD increases cardiovascular disease risk and reduced life expectancy, both of which would plausibly lower overall aging profiles summarized by aging-GIP.[56,57]

The remaining 30 exploratory mediators accounted for a relatively small proportion of the total effect (all $< 20\%$). Our findings extend the known roles of these lifestyle factors in linking AFS to aging. Notably, these mediators may reflect broader clusters of adiposity-related, inflammatory, emotional/mental health, or lifestyle factors rather than a direct mechanistic chain; thus, these findings are presented as exploratory signals consistent with potential pathways.

In summary, this study systematically assessed the comprehensive impact of early sexual behavior on aging. The identified mediators span multiple life stages, from prenatal to old age, reflecting the temporal breadth and complexity of the influence of AFS on aging. Given that various mediators may affect aging through diverse biological pathways, individual mediation proportions should be evaluated independently in practical applications.[58] Interestingly, some mediators exhibited high mediation proportions, likely due to the broad and severe impacts of early sexual behavior on physical and mental health.[5] The diversity of mediators and their substantial effects highlight the complexity of the AFS–aging relationship, indicating that efforts to promote healthy aging should not only emphasize sexual health education and the prevention of early sexual behavior but also target aging-related risk factors across the entire life course.

Based on our findings, we propose four concrete life-course interventions to mitigate the adverse effects of earlier AFS on aging: (1) School-based sexual health education: Integrate education on healthy sexual development, risk reduction, and life planning to delay early sexual initiation; (2) Targeted prevention for high-risk adolescents: Provide mental health support and life skills training for adolescents with early-life adversities to reduce the likelihood of early AFS; (3) Integrated programs for youth with early sexual debut: Address both risk behaviors (e.g., smoking) and mental health issues (e.g., ADHD) through coordinated healthcare and social services; (4) Mid-life screening and intervention: Implement regular screening for cardiovascular diseases, COPD, and frailty in adults with a history of earlier AFS, and provide personalized lifestyle modification programs (e.g., diet, exercise) to mitigate aging-related risks. These interventions align with full life-cycle theory, targeting key nodes in the causal pathway to promote healthy aging.

The main strengths of this study include the comprehensive and representative range of aging phenotypes, integration of genetic associations from multiple publicly available GWAS datasets, selection of candidate mediators spanning the full life cycle, and a rigorous MR study design, including standardized mediator selection criteria and strong causal inferences supported by multiple sensitivity analyses.

5. Limitations

Our study has several limitations. First, despite extensive sensitivity analyses, residual horizontal pleiotropy and dynastic effects cannot be fully excluded in MR studies of complex behavioral traits like AFS; thus, some effect estimates, especially counterintuitive ones, should be interpreted conservatively.[59] Second, all GWAS data were derived from individuals of European ancestry. The genetic architecture of AFS, its correlates, and the social meanings of early sexual debut may vary substantially across populations. This limits the immediate generalizability of the findings and underscores the need for replication in non-European cohorts. Third, the current two-step, two-sample MR design cannot model potential exposure-mediator interactions. However, the MR approach uses genetic variants fixed at conception and naturally randomly assigned to individuals as proxies for exposure and mediators,[19] largely mitigating bias from such interactions. Fourth, although this study included up to 145 mediators across four categories (lifestyles, behavioral emotions, physiological characteristics, and diseases), it did not capture all mediator pathways. Fifth, mediators were evaluated in a single-mediator framework; thus, mediation proportions are non-additive and should not be interpreted as independent contributions. Future work may apply joint multivariable approaches to estimate independent mediation effects. Sixth, gene–environment interactions could not be directly assessed with the available summary-level data; our estimates, therefore, reflect average genetic effects across environmental contexts. Future studies with individual-level data are warranted to test effect modification by factors such as educational attainment and social support.

6. Conclusion

From a full life cycle perspective, this MR study provides genetic evidence for a causal link between AFS and multidimensional aging phenotypes. Genetically predicted earlier AFS was causally associated with lower aging-GIP, shorter longevity and parental lifespan, and a higher frailty index, with no strong sex heterogeneity. In contrast, the observed associations between earlier AFS and healthspan as well as self-rated health were counterintuitive and require exploratory interpretation. We further identified 34 exploratory mediators spanning lifestyle, behavioral and emotional traits, physiological manifestations, and diseases in the causal pathway from AFS to aging-GIP, with the frailty index, miserableness, COPD, and ADHD each mediating more than 20% of the total effect. These core mediators cover key developmental stages from early life to late adulthood, which confirms that the impact of early sexual initiation on aging is a multi-pathway process.

This study advances life-course epidemiology by elucidating the long-term causal consequences of a key early-life behavioral event on late-life aging, and fills the knowledge gap in the underlying mechanisms linking AFS timing to aging trajectories. Our findings reinforce the public health significance of early sexual health education as a actionable strategy to shape healthy aging trajectories, and identify multiple life-stage targets for mitigating the adverse aging-related effects of early AFS—providing a genetic and mechanistic basis for developing life cycle-based public health interventions to promote healthy aging and reduce aging disparities. This work demonstrates the value of MR in uncovering the causal impacts of early-life behavioral traits on complex late-life aging phenotypes, offering a methodological framework for similar life-course epidemiological investigations.

CRediT authorship contribution statement

Kaixian Wang: Conceptualization, Formal analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Yizhan He:** Writing – review & editing. **Mengyao Yu:** Writing – review & editing. **Ziming Shao:** Writing – review & editing. **Zhen Wei:** Writing – review & editing. **Yingyue Xu:** Writing – review & editing. **Yazhuo Qi:** Writing – review & editing. **Wenyu Wang:** Writing – review & editing. **Xiao Li:** Writing – review & editing. **Xuehan Ren:** Writing – review & editing. **Long Sun:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. All the authors have read and approved the final version of this manuscript.

Ethics approval

This study used publicly available summary-level genome-wide association study (GWAS) data, with no access to individual-level participant information. Ethical approval for the original GWAS datasets was obtained by the respective study authors and consortia, and all details are reported in their original publications (cited throughout this manuscript).

Funding

The research was supported by the National Natural Science Foundation of China (72574129), and the Humanities and Social Sciences Fund of the Ministry of Education of China (24YJAZH134).

Data availability

All GWAS summary statistics analyzed in this study are publicly available for download by qualified researchers in Table 1 and Supplementary Table 1.

Declaration of Competing Interest

The authors declare no competing interests.

Declaration of Generative AI and AI-assisted technologies in the writing process

Not applicable.

Acknowledgments

The authors are grateful to the participants of all the GWAS used in this manuscript and the investigators who made these GWAS data publicly available.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.hcr.2026.100064.

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