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Long-term impact of adherence to muscle-strengthening guidelines on inflammation markers: a 17-year follow-up study with obesity parameters as mediators

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ABSTRACT

Objective To evaluate the relationship between adherence to muscle-strengthening guidelines in young adulthood and inflammation markers over a 17-year follow-up period. Additionally, it aims to examine whether body mass index (BMI) and waist circumference (WC) act as mediators in this relationship.

Methods The study analysed data from young adults aged 18–26 years who participated in waves III (2001–2002), IV (2008–2009) and V (2016–2018) of the Add Health Study. Adherence to muscle-strengthening guidelines was self-reported, and participants were classified as adherent if they engaged in strength training ≥2 days per week across all waves. Venous blood samples were collected at participants' homes to measure high-sensitivity C reactive protein (hs-CRP) levels and various cytokine concentrations, including interleukin (IL)–6, IL-1beta, IL-8, IL-10 and tumour necrosis factor-alpha (TNF-α). A global inflammation score was also calculated using z-scores of these markers.

Results A total of 2320 individuals participated (60.8% females). Participants adhering to muscle-strengthening guidelines exhibited significant reductions in hs-CRP, IL-6 and the inflammation z-score, with mean difference (MD) of −1.556 mg/L (95% CI BCa −2.312 to −0.799), −0.324 pg/mL (95% BCa CI −0.586 to −0.062), and −0.400 (95% BCa CI −0.785 to −0.035), respectively. Mediation analysis revealed that BMI and WC levels at wave V significantly mediated the relationship between strength training and inflammation z-score, with significant indirect effects of −0.142 (95% CI −0.231 to −0.055) for BMI and −0.210 (95% CI −0.308 to −0.124) for WC.

Conclusion Adherence to muscle-strengthening guidelines alone may not be sufficient to achieve a notable decrease in inflammation without concurrent reductions in these obesity parameters.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous research has established that regular muscle-strengthening exercises can reduce inflammation and improve overall health. However, the relationship between strength training, inflammation, and obesity-related factors like body mass index (BMI) and waist circumference (WC) has not been fully elucidated, especially over long-term follow-up periods.

WHAT THIS STUDY ADDS

⇒ Adherence to muscle-strengthening guidelines is linked to significant reductions in inflammation markers over 17 years. However, the anti-inflammatory benefits are significantly mediated by reductions in BMI and WC, suggesting that strength training alone may not be sufficient to reduce inflammation without concurrent weight management.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the need for integrated public health strategies that combine strength training with obesity management to maximise the reduction of inflammation and its associated risks. It also suggests that future research should explore personalised interventions that address both exercise and weight control to prevent chronic inflammatory diseases.

INTRODUCTION

Muscle-strengthening training during adulthood is widely acknowledged for its benefits in improving physical fitness and overall health.[1 2] Recent research has increasingly focused on its broader implications for metabolic health, particularly its potential impact on inflammation.[3] Chronic inflammation is a critical factor in the development and progression of various diseases, including cardiovascular conditions, diabetes and obesity.[4] Given that lifestyle factors such as physical activity play a crucial role in modulating inflammatory responses, it is essential

to understand how different types of exercise affect inflammation.[5 6]

In addition to the WHO recommendation of 150 min of moderate-intensity exercise per week, it is advised that individuals aged 18 years and above engage in muscle-strengthening exercises two times a week.[7] Muscle-strengthening exercise, which includes using weight machines, exercise bands, hand-held weights or body weight (eg, push-ups or sit-ups) and is typically performed during leisure time in gyms or at home,[8] improves skeletal muscle strength, power, endurance and mass when done regularly.[2] Despite the growing body of evidence supporting the benefits of muscle-strengthening exercises due to their potential health benefits,[9] there remains a need to clarify their specific effects on inflammation markers.[2]

Research indicates that muscle-strengthening exercise can lead to reductions in inflammatory markers such as high-sensitivity C reactive protein (hs-CRP) and various cytokines.[3] These benefits are thought to arise through multiple mechanisms, including the reduction of body fat[10] and enhancement of metabolic health.[1] Adipose tissue, particularly visceral fat, is a significant source of proinflammatory cytokines,[11] and reducing body fat through exercise can mitigate these inflammatory effects.[12–15]

Obesity-related parameters, such as body mass index (BMI) and waist circumference (WC), could be critical mediators in the relationship between physical activity and inflammation. By improving these parameters, muscle-strengthening training may exert its anti-inflammatory effects indirectly through these parameters.[3 16 17] However, the long-term impacts of consistent adherence to muscle-strengthening guidelines on inflammation markers require further investigation. Understanding how muscle-strengthening adherence is related to inflammation and the role of obesity in this process can provide valuable insights into effective strategies for managing and reducing chronic inflammation through lifestyle interventions. Therefore, this study aimed to evaluate the relationship between adherence to muscle-strengthening guidelines in young adulthood and inflammation markers over a 17-year follow-up period and to examine whether BMI and WC serve as mediators in this relationship.

METHODS

Participants

This is a prospective cohort study with 17-year follow-up, the reporting of which followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[18] It uses data from the Add Health study, which comprises a nationally representative sample of adolescents in grades 7–12 across the USA. Participants were followed from adolescence into adulthood.[19] In the present study, we used data from waves III (2001–2002), IV (2008–2009) and V (2016–2018), because these specific waves included information on muscle-strengthening training practices. Unfortunately, waves I and II lacked the necessary data on muscle-strengthening activities and were, therefore, not included in the analysis. After excluding missing data and participants who had experienced infectious or inflammatory diseases in the last 4 weeks—including gum disease/tooth loss, active infections, injuries, acute illnesses, surgeries or active seasonal allergies—we included 2320 individuals in the analysis.

The Add Health study received approval from the Institutional Review Board at the University of North Carolina at Chapel Hill. Authorisation to conduct secondary analyses was granted by the Ethics Committee of the University Hospital of Navarra (PI_2020/143).

Anthropometry

Height, body weight and WC were measured by field examiners using standardised protocols (details are available on the Add Health website, https://addhealth.cpc.unc.edu/documentation/codebooks/). BMI was then calculated as weight in kilograms divided by height in m^2.

Inflammation biomarkers

At wave V, venous blood samples were collected from participants in their homes. hsCRP levels were measured in serum using the Siemens BNII/BN Prospec System (Siemens Healthcare Diagnostic Products GmbH, Marburg, Germany) with a particle-enhanced immunonephelometric assay. hsCRP values were coded as a binary indicator of high inflammation if levels exceeded 3 mg/L.[20] Additionally, cytokine concentrations, including interleukin (IL)−6, IL-1beta, IL-8, IL-10 and tumour necrosis factor-alpha (TNF-α), were assessed using the Meso Scale Diagnostics (MSD) V-PLEX Human Cytokine assay on the MSD QuickPlex 120 platform, enabling simultaneous and accurate detection of multiple cytokines.

Finally, an overall inflammation score was calculated using z-scores for the above markers. Before calculating the z-scores, the variables were logarithmically transformed to normalise their distribution. After the transformation, z-scores were computed for each marker. In the case of IL-10, the values were inverted (multiplied by −1) to align with the direction of the other markers, as IL-10 is an anti-inflammatory cytokine, whereas the other markers represent proinflammatory activity. The final score was obtained by summing the z-scores of all the markers.

Muscle-strengthening training

Participants answered the following question to determine their weekly muscle-strengthening training frequency: 'In the past 7 days, how many times did you participate in gymnastics, weightlifting or strength training?' Adherence to guidelines was defined as participating in strength training 2 or more days per week[7] across all three waves.

Definitions of covariates

Sociodemographic information, including age, sex and race/ethnicity, was collected through in-home

questionnaires. Race/ethnicity was categorised into four groups: white, black or African American, American Indian or Alaska Native and Asian.

In wave V, alcohol consumption was evaluated by asking, 'In the past 30 days, on how many days did you consume alcohol (beer, wine, liquor)?'. Based on their responses, participants were grouped into the following categories: 'none', '1 or 2 days in the past 12 months', 'once a month or less (3 to 12 times in the past 12 months)', '2 or 3 days a month', '1 or 2 days a week', '3–5 days a week' and 'every day or almost every day'. Smoking behaviours were assessed by asking adults, 'In the past 30 days, on how many days did you smoke cigarettes?'. Finally, fast food consumption was evaluated by asking, 'In the last 7 days, on how many days did you eat at a fast-food type place?'.

Statistical analysis

Descriptive information is shown as numbers and percentages for categorical variables and mean and SD for continuous variables at wave V. Mann-Whitney U tests were conducted for comparisons of continuous variables (BMI, WC, fast food consumption) and χ^2 tests for categorical variables (sex distribution) were conducted.

We assessed MDs in inflammatory biomarkers at wave V among those who did and did not meet muscle-strengthening guidelines at waves III, IV and V. Generalised linear models with Gaussian distribution were conducted to control for potential confounding variables and to assess the main effects and interactions. Model 1 included adjustments for sex, race/ethnicity, age at follow-up, fast food consumption, cigarette smoking and alcohol consumption at wave V. Models 2 and 3 further included WC or BMI as covariates, respectively. Previously, we evaluated the interaction with sex to determine if the relationship differed between males and females. Since no significant interactions were found (ie, the interaction was between adherence to muscle-strengthening guidelines and sex in relation to overall inflammation: p=0.378), data for both sexes were analysed together. All model assumptions were checked, including independence, linearity, normality and homoscedasticity. Given that error terms were not normally distributed, a bias-corrected and accelerated (BCa) bootstrap technique with 5000 replicates and resampling of dependent variables with replacement was used as a non-parametric approach. This method is preferred over traditional transformations because it does not rely on distributional assumptions and provides more robust CIs by adjusting for bias and skewness, offering more accurate inference under non-normal conditions.[21]

Generalised linear models with a binomial distribution were used to determine the odds of having high levels of hs-CRP (ie, ≥3 mg/L) in relation to meeting muscle-strengthening guidelines, incorporating the previously mentioned adjustments and variables.

To assess the influence of obesity parameters at follow-up on the relationships between adherence to meeting muscle-strengthening guidelines (independent variables) and inflammation z-score (as dependent variable), we employed adjusted generalised linear regression mediation models. Following Baron and Kenny's procedure, we used 5000 bootstrapped samples with the PROCESS package. All analyses were conducted in R (V.4.3.2) and RStudio (V.2023.09.1+494). Statistical significance was set at two-sided p<0.05.

RESULTS

Table 1 presents the demographic characteristics at wave V for individuals who adhered to muscle-strengthening guidelines (17.3%) compared with those who did not. Adults who adhered had lower BMI (31.76 vs 35.66 kg/m², p<0.001) and WC (94.36 vs 108.33 cm, p<0.001). They also consumed less fast food (1.18 vs 2.25 servings in the last week, p<0.001). Additionally, significant differences were found in sex distribution (68.1% females in non-adherents vs 32.1% in adherents, p<0.001) and racial/ethnic composition, while alcohol and cigarette consumption patterns were similar between the groups.

Table 2 summarises the MD in inflammation parameters at wave V for participants adhering to muscle-strengthening guidelines compared with those who did not. Model 1 shows significant differences in hs-CRP, with an MD of −1.556 mg/L (95% BCa CI −2.312 to −0.799, p<0.001), and in the inflammation z-score, with an MD of −0.400 (95% BCa CI −0.785 to −0.035, p=0.022). In contrast, model 2 and model 3 display non-significant differences in these parameters, with hs-CRP MDs of −1.056 (95% BCa CI −1.755 to 0.057, p=0.053) and −0.509 (95% BCa CI −1.192 to 0.173, p=0.144), respectively, and z-scores of −0.348 (95% BCa CI −0.723 to 0.077, p=0.169) and −0.301 (95% BCa CI −0.680 to 0.077, p=0.119), respectively. For IL-6, model 1 shows a trend towards significance with an MD of −0.324 pg/mL (95% BCa CI −0.586 to −0.062, p=0.015), but the results are less clear in the other models. Other parameters, such as IL-1beta, IL-8, IL-10 and TNF-α, did not show significant differences across the models.

Mediation analysis revealed that both BMI and WC levels at wave V significantly mediate the relationship between adherence to muscle-strengthening guidelines and inflammation z-score (figure 1). Adherence to muscle-strengthening guidelines resulted in a significant reduction in BMI (unstandardised beta coefficient (B)=−1.759, 95% BCa CI −3.111 to −0.407; p=0.011), and BMI was associated with inflammation (B=0.081, 95% BCa CI 0.069 to 0.092; p<0.001). The direct effect of adherence to muscle-strengthening guidelines on inflammation was reduced from (B=−0.441, 95% BCa CI −0.832 to −0.051; p=0.027) to (B=−0.301, 95% BCa CI −0.680 to 0.077; p=0.119) after including BMI, indicating a significant indirect effect (B_{ind}=−0.142, 95% BCa CI −0.223 to −0.061). Similarly, WC also mediated this relationship. Adherence to muscle-strengthening guidelines was significantly associated with a reduction in WC (β=−6.599, 95% BCa CI −9.752 to −3.447; p<0.001), and WC positively associated with inflammation (B=0.032,

Table 1 Demographic characteristics of the individuals at wave V according to adherence to muscle-strengthening guidelines

	Adherence to guidelines n=401	Non-adherence to guidelines n=1919	P value
Age, years	37.86 (2.07)	37.58 (1.81)	0.232
Female sex, %	32.1	68.1	<0.001
Body mass index, kg/m^2	31.76 (7.36)	35.66 (9.34)	<0.001
Waist circumference, cm	94.36 (20.69)	108.33 (21.37)	<0.001
Race/ethnicity, %			0.322
White	64.3	77.2	
Black or African American	35.7	22.7	
American Indian or Alaska Native	0	0.9	
Asian	0	3.5	
Fast food consumption last week	1.18 (1.19)	2.25 (2.44)	<0.001
Cigarettes smoked last 30 days	5.14 (11.01)	5.89 (11.52)	0.071
Alcohol consumption			
None, %	14.3	8.7	0.562
1 or 2 days in the past 12 months, %	17.9	16.3	
Once a month or less, %	25.0	19.5	
2 or 3 days a month, %	7.1	17.7	
1 or 2 days a week, %	17.9	18.5	
3–5 days a week, %	14.3	8.7	
Every day or almost every day, %	0	3.5	

Data presented as means and SD for continuous variables. P values were considered significant when<0.05. Statistical tests used to generate p values included Mann-Whitney U tests for continuous variables and χ^2 tests for categorical variables.

95% BCa CI 0.027 to 0.037; p<0.001). The direct association between adherence to muscle-strengthening guidelines and inflammation was significant without the mediator (B=−0.441, 95% BCa CI −0.832 to −0.051; p=0.027), but it became non-significant after including WC (B=−0.232, 95% BCa CI −0.611 to 0.145; p=0.231), indicating a significant indirect effect (B_{ind}=−0.210, 95% BCa CI −0.308 to −0.124).

DISCUSSION

Our research highlights the significant association between adhering to muscle-strengthening guidelines and inflammation markers. The negative association observed in these markers suggests that muscle-strengthening exercise may contribute to lower inflammation levels, potentially benefiting long-term health. The mediation analysis further reveals that these effects are partially mediated by the negative association with obesity-related parameters, specifically BMI and WC.

These findings emphasise the significant role of adhering to muscle-strengthening guidelines on systemic inflammation, particularly hs-CRP, IL-6, and the inflammation z-score. This finding aligns with previous research pointing out that muscle-strengthening training can significantly reduce inflammatory markers.[3] According to the 2023 Scientific Statement from the American Heart Association, the effect of muscle-strengthening training on inflammation markers is inconsistent and typically focuses on the analysis of hs-CRP and IL-6.[2] It is also important to highlight that most studies in this area are based on supervised strength training and are typically conducted in populations with obesity[22] and/or type 2 diabetes.[14 23 24] Our results add to this body of evidence by emphasising that consistent adherence to muscle-strengthening guidelines could contribute to lower inflammation levels, highlighting the importance of integrating resistance exercises into public health recommendations to mitigate chronic inflammation and associated health risks. It is well established that muscle-strengthening exercise can exert anti-inflammatory effects through several mechanisms. During strength training, muscle contractions release myokines, such as IL-6, IL-10 and IL-1ra, which possess anti-inflammatory properties.[25 26] Additionally, regular muscle-strengthening training leads to increased muscle mass and reduced body fat, both of which contribute to improved metabolic health and a reduction in systemic inflammation.[27 28] Our findings suggest that a regular weekly strength training habit may benefit health by reducing inflammation in the general population.

The mediation analysis in our study reveals that both BMI and WC levels at wave V significantly mediate the

Table 2 Mean differences in inflammation parameters at wave V comparing subjects adhering to muscle-strengthening guidelines versus those not adhering

	Model 1			Model 2			Model 3		
	MD	95% BCa CI	P value	MD	95% BCa CI	P value	MD	95% BCa CI	P value
Hs-CRP, mg/L	−1.556	−2.312 to −0.799	<0.001	−1.056	−1.755 to 0.057	0.053	−0.509	−1.192 to 0.173	0.144
hs-CRP≥3 mg/L	*0.479*	*0.363 to 0.634*	*<0.001*	*0.622*	*0.459 to 0.843*	*0.002*	*0.536*	*0.395 to 0.728*	*<0.001*
IL-1beta, pg/mL	−0.083	−0.240 to 0.074	0.300	−0.095	−0.254 to 0.063	0.240	−0.083	−0.244 to 0.079	0.315
IL-6, pg/mL	−0.324	−0.586 to −0.062	0.015	−0.252	−0.511 to 0.006	0.056	−0.230	−0.492 to 0.033	0.086
IL-8, pg/mL	−1.568	−10.148 to 7.013	0.720	−5.093	−13.640 to 3.455	0.243	−4.259	−12.894 to 4.377	0.334
IL-10, pg/mL	0.019	−0.018 to s10.056	0.324	−0.023	−0.059 to 0.014	0.223	−0.015	−0.052 to 0.022	0.441
TNF-α, pg/mL	−0.035	−0.316 to 0.245	0.806	−0.003	−0.282 to 0.276	0.985	−0.090	−0.374 to 0.194	0.535
Inflammation, z-score	−0.400	−0.785 to −0.035	0.022	−0.348	−0.723 to 0.077	0.169	−0.301	−0.680 to 0.077	0.119

Reference: non-adherence.
Italicised results show relative risk values.
Model 1: Analyses were adjusted for sex, race/ethnicity, age at follow-up, fast food consumption, cigarettes smoked and alcohol consumption at follow-up.
Model 2: Model 1 + waist circumference.
Model 3: Model 1 +body mass index.
BCa, bias-corrected and accelerated; BCa, bias-corrected and accelerated; hs-CRP, high-sensitivity c-reactive protein; IL, interleukin; MD, mean difference; TNF, tumour necrosis factor.

relationship between adherence to muscle-strengthening guidelines and inflammation. The direct effect of adherence to muscle-strengthening guidelines on inflammation becomes less significant when adjusting for BMI and WC, highlighting their role as crucial intermediaries. This finding is supported by previous research, such as Vieira *et al*,[17] which indicated that improvements in body composition, particularly reductions in trunk fat, predict training-related reductions in hs-CRP. This is also consistent with the findings of Church *et al*,[29] who found that their randomised controlled exercise trial, conducted with sedentary individuals having high hs-CRP levels, showed that exercise alone, without accompanying weight loss, did not lead to a decrease in hs-CRP levels. Furthermore, the role of body composition as a mediator is reinforced by a previous review,[15] which reported that exercise training alone, without accompanying weight loss, does not consistently reduce inflammatory biomarker concentrations. This underscores the importance of not only engaging in regular resistance training but also focusing on weight management and fat reduction to achieve significant reductions in systemic

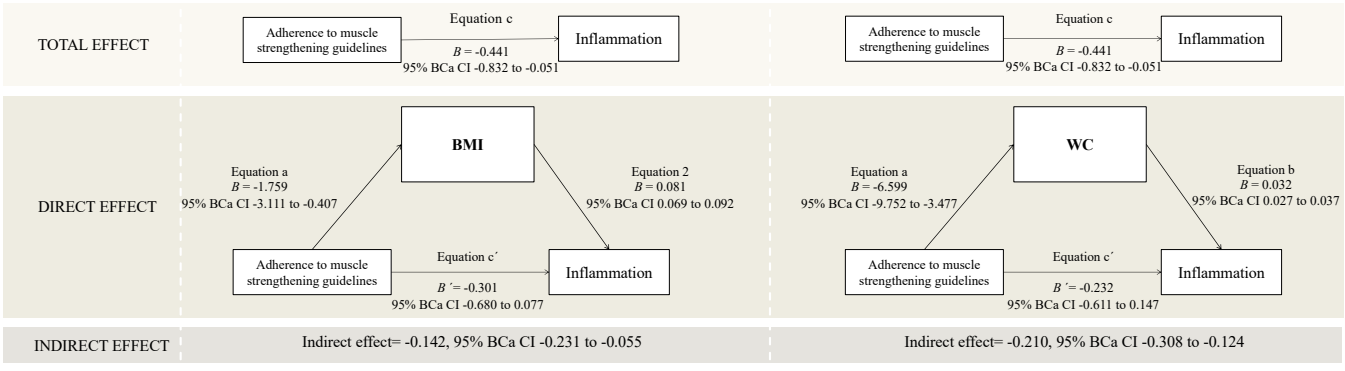

Figure 1 Body mass index and waist circumference as mediators of the influence of adherence to muscle-strengthening guidelines on inflammation. The direct effect is calculated as the relationship between the independent variable and the dependent variable while controlling for the mediator, while the indirect effect is calculated as the product of the effect of the independent variable on the mediator and the effect of the mediator on the dependent variable. B, unstandardised beta coefficient; BCa, bias-corrected and accelerated; BMI, body mass index; WC, waist circumference.

inflammation. Therefore, because of the strong association between inflammation and adiposity,[30] in order to resolve whether increasing physical activity has benefits on inflammation, it is important to delineate the effects of exercise both with and without fat loss.

Clinical implications

The findings of this study suggest that while muscle-strengthening exercises can be beneficial, their full anti-inflammatory potential may only be realised when combined with strategies that also target weight management. Thus, clinicians should consider promoting not only regular strength training but also additional lifestyle interventions that address both physical activity and weight management. For patients, particularly those at risk of chronic inflammatory conditions such as cardiovascular disease or type 2 diabetes, it may be advisable to integrate muscle-strengthening routines with dietary interventions and other weight management strategies to optimise inflammatory profiles. Our results also reinforce the need for personalised approaches in clinical settings, where exercise prescriptions are tailored to individual body composition and metabolic health.

Limitations

This study has several limitations that should be noted. First, we lack detailed information on the duration and intensity of muscle-strengthening training, which are important factors that could influence the inflammation biomarkers and the extent of the observed effects. Additionally, recall and social desirability biases may have affected the accuracy of the self-reported data on adherence to muscle-strengthening guidelines. Additionally, we did not have direct measurements of body composition, such as those obtained through dual-energy X-ray absorptiometry or MRI, which would provide more precise data on fat mass and distribution. Despite WC being a good indicator of visceral fat, as corroborated by previous studies,[31 32] our reliance on indirect measures limits the precision of our findings. Therefore, future research should incorporate direct measures of fat mass and distribution to better understand the mechanisms linking exercise to inflammation.

CONCLUSION

Our study underscores the significant role of adhering to muscle-strengthening guidelines in reducing systemic inflammation markers, such as hs-CRP, IL-6, and overall inflammation. The mediation analysis suggests that these anti-inflammatory effects are partially mediated by obesity-related parameters, specifically BMI and WC. These findings support the inclusion of muscle-strengthening exercises in public health recommendations as a strategy to mitigate chronic inflammation and associated health risks, emphasising the importance of both muscle-strength training and weight management for optimal health outcomes.

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Contributors AG-H and JL-G conceptualised and designed the study, data collection instruments, collected data, carried out the analyses, and wrote the manuscript (original draft). AG-H and YE wrote the manuscript (original draft). AG-H carried out the analyses. YE, RY-S, JO-A and JP-H critically reviewed the manuscript for important intellectual content. AG-H is the guarantor of this article, and he accepts full responsibility for the work, had access to the data, and controlled the decision to publish. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patients.

Ethics approval The Add Health study received approval from the Institutional Review Board (IRB) at the University of North Carolina at Chapel Hill. Authorisation to conduct secondary analyses was granted by the Ethics Committee of the University Hospital of Navarra (PI_2020/143). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Due to our data protection agreements with the participating cohort study, we are unable to share individual-level data with third parties. According to Add Health's data access policy, researchers can submit data requests to the steering committee. These requests will be reviewed promptly for confidentiality, data protection, and intellectual property considerations, and will not be unreasonably denied. Researchers registered with Add Health can apply for access to its database by submitting an application (https://data.cpc.unc.edu/projects/2/view).

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