

Body size changes and social determinants: Effects on rheumatoid arthritis, complications, and life expectancy in middle-aged and older adults

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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Adverse body size changes, especially leading to adult obesity, increase rheumatoid arthritis (RA) risk.
- This increased RA risk was compounded by unfavorable social determinants of health (SDOHs).
- These interactive effects were consistently associated with an increased risk of post-RA complications.
- Individuals with unfavorable SDOHs had shorter life expectancies across all body size change groups.
- Public health strategies are needed to address adverse body size changes and socioeconomic disparities.

Body size changes and social determinants: Effects on rheumatoid arthritis, complications, and life expectancy in middle-aged and older adults

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Little is known about the combined effects of body size changes and social determinants of health (SDOHs) on rheumatoid arthritis (RA). In this study, we assessed these effects on (1) the incidence and age at onset of RA; (2) complications after RA diagnosis; and (3) life expectancy in 302,239 middle-aged and older adults from the UK Biobank. Childhood body size data at age 10 were collected through a questionnaire. Adulthood body size was assessed using body mass index (BMI), the waist-to-hip ratio (WHR), and the waist-to-height ratio (WHtR). The SDOHs were constructed with 20 items, with each item dichotomized into advantaged and disadvantaged levels. Cox proportional hazard models and life tables were applied to calculate adjusted hazard ratios (HRs) and predict life expectancy. During a median follow-up period of 12.5 years, 3,649 participants developed RA. Adverse body size changes, particularly those leading to obesity in adulthood BMI or high WHR/WHtR in adulthood, were associated with an increased risk of RA. These risks were further amplified by unfavorable SDOHs, with hazard ratios ranging from 2.18–2.92. These interactive effects were consistently associated with an elevated risk of RA onset across age groups and post-RA complications. Notably, individuals with unfavorable SDOHs experienced the shortest life expectancies compared with those with favorable SDOHs across all body size change groups. In conclusion, adverse body size changes and unfavorable SDOHs are significantly associated with an increased risk of new-onset and age at onset of RA, post-RA complications, and reduced life expectancy.

INTRODUCTION

As one of the most prevalent chronic inflammatory diseases, rheumatoid arthritis (RA) affects 0.5–1% of the global population. Its incidence increases with age, with onset commonly occurring between 60 and 70 years.^{1–3} The disease progressively destroys and deforms joints, causes widespread pain, triggers cardiovascular disease (CVD) and pulmonary damage, impairs daily functioning, and leads to long-term disability and premature death.^{3,4} With global aging, the prevalence of RA is expected to increase substantially, imposing significant economic and societal burdens. This demographic shift underscores the urgency of understanding and addressing the risk factors associated with RA development and progression.

Overweight and obesity are recognized as potential risk factors for RA.⁵ Several meta-analyses have consistently shown that a high body mass index (BMI) is associated with a 3–12% increased risk of RA.^{6,7} While BMI is a common measure of body size, it does not fully capture the complexities of body fat distribution and its metabolic consequences; therefore, other anthropometric measures, such as the waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR), provide additional insights by assessing abdominal obesity, which is more closely linked to metabolic disturbances and inflam-

mation.^{8,9} Despite their potential relevance and the comprehensive understanding they offer alongside BMI, evidence linking these alternative measures specifically to RA risk remains limited. Furthermore, understanding how body size changes over time is essential, as static measurements may not fully reflect the lifelong impact of obesity on RA development. Given that the prevalence of childhood obesity has tripled over the past 30 years, concerns arise that children with obesity might carry this condition into adulthood, thus leading to RA development later in life.¹⁰ A prospective cohort study linking childhood adiposity to an increased risk of RA underscores the importance of investigating body size changes from childhood to adulthood to understand how lifelong patterns of body size influence RA risk, yet this area remains largely unexplored.¹¹

Social determinants of health (SDOHs) also play a critical role in influencing health outcomes.^{12,13} SDOHs are increasingly recognized as upstream drivers of preventable health inequities.¹⁴ The Healthy People 2030 initiative emphasizes the importance of the SDOHs in reducing health disparities and proposes a framework encompassing five domains: economic stability, education access and quality, healthcare access and quality, the neighborhood and built environment, and the social and community context.¹⁵ While extensive literature exists on the relationships between SDOHs and various diseases, research specifically addressing the association between SDOHs and RA remains limited. The few studies available often have limitations such as small sample sizes,^{16,17} a lack of longitudinal data,¹⁸ and a narrow focus on socioeconomic statuses (SESS).¹⁹ However, SDOHs encompass a broader spectrum of factors beyond SESS, necessitating a more comprehensive approach. The coexistence and interconnected nature of various disadvantaged SDOH factors create complex pathways for health outcomes. Consequently, simultaneously considering multiple SDOH factors and quantifying their combined impacts offers a more nuanced understanding of their influence on RA-related outcomes. Failure to account for the synergistic effects of multiple social risk factors may impede the identification of vulnerable populations and compromise the efficacy of interventions aimed at reducing the RA burden and improving outcomes.

Significant gaps persist regarding the combined effects of body size changes and SDOHs on the incidence of RA and the age at its onset. Understanding these dynamics could reveal novel risk stratification methods and inform precision medicine approaches in RA care. Moreover, the impacts of these combined factors on RA-associated complications, mortality, and life expectancy remain underexplored. RA patients experience a range of manifestations and comorbidities, including CVD, lung disease, metabolic syndrome, osteoporosis, and anemia, which contribute to a reduction in life expectancy compared with that of the general population.²⁰ The extent to which body size changes and SDOHs influence the development and progression of these complications, particularly in the context of an aging

global population, represents a critical area for further investigation. Elucidating these relationships could inform more effective interventions to reduce the RA burden, improve quality of life, and extend life expectancy for individuals with RA.

Therefore, this study aims to investigate the combined effects of body size changes and social determinants on (1) the incidence and age at onset of RA; (2) complications after RA diagnosis; and (3) life expectancy in middle-aged and older adults.

MATERIALS AND METHODS

Study population

The UK Biobank is a large-scale prospective cohort study that recruited over 500,000 individuals aged 37 to 73 years from the general populations of England, Wales, and Scotland between 2006 and 2010. Detailed information regarding the study design, methods, and data collection has been previously published.²¹ Participants were recruited through 22 assessment centers nationwide. At enrollment, they completed a touch-screen questionnaire on their lifestyle, childhood body size, and health-related factors, participated in a clinical interview, and underwent physical examinations, with biological samples collected. This study used data from the UK Biobank Resource, approved by the North West Multicenter Research Ethics Committee (REC reference 21/NW/0157). All participants provided informed consent through electronic signatures at the baseline assessment, and the UK Biobank study was approved by the North West-Haydock Research Ethics Committee (reference 21/NW/0157).

Out of 502,193 participants in the UK Biobank, 199,954 were excluded because of factors including age under 45 years, missing data on childhood body size or health measures, absence of RA polygenic risk scores, prevalent RA at baseline, or incomplete data on social determinants of health. After these exclusions were applied, 302,239 participants remained for the main analysis. For each complication, we excluded prevalent cases at baseline and further excluded cases where complications occurred without a prior RA diagnosis or developed before or concurrent with RA. The selection process is presented in the flowchart (Figure S1).

Body size change

Childhood body size was categorized into three groups: 'thinner', 'average', and 'plumper' on the basis of the participants' response to the following question: "When you are 10 years old, compared with average, would you describe yourself as thinner, about average, or plumper?" The validity of this measure has been supported by previous studies investigating polygenic scores against measured BMI from British and Norwegian birth cohorts.^{22,23}

In adulthood, body weight, height, waist circumference, and hip circumference were measured by trained staff during the enrollment assessment using standardized procedures.²⁴ Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in meters (kg/m^2). The WHR was calculated by dividing waist circumference by hip circumference. The WHtR was calculated by dividing waist circumference by height. These metrics were categorized into groups: BMI as normal ($<25.0 \text{ kg}/\text{m}^2$), overweight ($25.0\text{--}<30.0 \text{ kg}/\text{m}^2$), or obese ($\geq 30.0 \text{ kg}/\text{m}^2$); WHR as low (men: <0.91 , women: <0.79), intermediate (men: $0.91\text{--}<0.96$, women: $0.79\text{--}<0.85$), or high (men: ≥ 0.96 , women: ≥ 0.85); and WHtR as low (<0.5), intermediate ($0.5\text{--}<0.6$), or high (≥ 0.6).^{25–27}

Thus, each body size measurement has 9 changes. For example, thinner childhood body size to normal, overweight, or obese adulthood BMI; average childhood body size to normal, overweight, or obese adulthood BMI; plumper childhood body size to normal, overweight, or obese adulthood BMI. For the multistate analysis and life expectancy analysis, we categorized BMI, WHR, and WHtR into binary groups and collapsed childhood body size into two groups, 'thinner/average' and 'plumper', resulting in 4 changes. The detailed measurement procedures and additional categorization information can be found in Method S1.

Social determinants of health

The SDOHs encompass five key domains: healthcare access and quality, education access and quality, the social and community context, economic stability, and the neighborhood and built environment.^{12,15} In this study, 20

items for the SDOHs within 5 domains were selected according to the Healthy People 2030 objectives and previous studies.^{12,15,28} All the information was collected by questionnaires or linked to the Lower-layer Super Output Area code to the index of multiple deprivation scores in the UK. Further details are available in Method S2 and Tables S1–S2.

Polygenic risk score

The genotyping procedures and quality control protocols for the UK Biobank have been reported elsewhere.²⁹ For this analysis, the polygenic risk score (PRS) for RA was derived from the UK Biobank PRS Release available through the Research Access Platform. Using Bayesian methods, the PRS was calculated from meta-analyses of summary statistics obtained from external GWASs (standard PRS), summing per-variant posterior effect sizes multiplied by allele dosage. Further details are available at <https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=5202> and <https://www.medrxiv.org/content/10.1101/2022.06.16.22276246v2>.

Covariates

Age at baseline was calculated from birth and recruitment dates. The participants' sex and residential area (urban or rural) were recorded. Smoking status was categorized as "current", "former", or "never"; alcohol intake frequency as " ≥ 3 times/week", " < 3 times/week", or "never"; sleep duration as " < 7 h per day", " $7\text{--}8$ h per day", or " > 8 h per day". Physical activity was categorized as high, moderate, or low according to the International Physical Activity Questionnaire. A healthy diet score was defined on the basis of cardiometabolic disease priorities, with a higher score indicating healthier habits.³⁰ Definitions of each component of a healthy diet score are described in Table S3.

Ascertainment of outcome and life expectancy

The outcomes of interest were RA, complications after RA diagnosis and all-cause mortality. All outcomes were ascertained through linkage sources from primary care, hospital inpatient, and death registry records. Details for the disease codes are shown in Table S4. The follow-up time was calculated from the date of the assessment center's visit until the date of death, the date of loss to follow-up or the end of the study (30 September 2021 for England and Wales and 31 October 2021 for Scotland).

To estimate healthy life expectancy, we constructed life tables for individuals aged 50 to 100 years using three primary estimates:³¹ (i) population mortality rates by age and sex from the Office for National Statistics,³² (ii) sex-specific hazard ratios (HRs) for all-cause mortality on the basis of combinations of frailty and healthy diets, and (iii) the prevalence of each frailty-diet combination by sex. Details of the methods used for estimating life expectancy are described in Method S3.

Statistical analysis

Descriptive characteristics by frailty status are presented as frequencies with percentages for categorical variables and means with standard deviations (SDs) for continuous variables. Missing covariate data were imputed with multiple imputations via chained equations.

To explore the combined effects of body size change and SDOHs with incident RA, Cox proportional hazard regression models were employed to assess hazard ratios (HRs) and corresponding 95% confidence intervals (CIs), with follow-up time used as the underlying timescale. Two models were constructed to adjust for potential confounders. Model 1 was adjusted for age at recruitment, sex, region, smoking status, alcohol consumption frequency, sleep duration, healthy diet score, and physical activity. Model 2 was further adjusted for RA PRS, the genotyping array, and the first 10 principal components of ancestry. We found no collinearity issues through a correlation matrix analysis and the calculation of the variance inflation factor. Additionally, we analyzed how body size changes and SDOHs interact to influence incident RA, stratified by age and sex.

To assess the dose-response relationships between adulthood body size indicators and RA risk within each childhood body size category, we examined HR and 95% CIs using restricted cubic splines (RCSs), with four knots positioned at the 5th, 35th, 65th, and 95th percentiles of each exposure.

We divided the participants into 3 age groups (<60 , 60 to <70 , and ≥ 70 years) and explored the combined effects of body size change and SDOHs on

the age at onset of RA. Participants could move into successive age groups over time until the occurrence of RA or censoring (due to death or the end of follow-up). Thus, as they aged, individuals could contribute to more than one age group, as described earlier.³³ We employed stratified Cox proportional hazards models using the counting process method, with age as the timescale. Details are described in [Method S4](#).

To investigate the joint associations of body size change and SDOHs with post-RA complications, including CVD, lung disease, chronic kidney disease (CKD), osteoporosis, and anemia, we conducted fully adjusted models. For each complication, we excluded existing cases at baseline and cases where complications occurred without a prior RA diagnosis or developed before or concurrently with RA.

We performed several supplementary analyses. First, we conducted independent analyses of body size changes on incident RA and age at onset of RA. Second, we examined the combined effects of body size change and SDOHs on all-cause mortality. Third, we applied multistate models to explore the joint effects of body size change and SDOHs on the transition from being RA-free to developing RA and, ultimately, all-cause mortality.³⁴⁻³⁶ For cases where participants entered multiple stages on the same day, we adjusted the entry date of the preceding state by subtracting 0.5 days from the date of the subsequent state body size change and SDOHs on the transition from being RA-free to developing RA and, ultimately, all-cause mortality.³⁴⁻³⁶ For cases where participants entered multiple stages on the same day, we adjusted the entry date of the preceding state by subtracting 0.5 days from the date of the subsequent state.^{37,38} Fourth, to isolate the independent effects of childhood or adulthood body size on incident RA, we performed separate analyses to identify how each contributes to RA risk. Fifth, we performed mediation analysis to explore the role of C-reactive protein (CRP) as a mediator in the associations between body size changes, SDOHs, and RA, further clarifying the potential inflammatory pathways involved. Sixth, we explored the combined effects of body size change and the RA PRS with incident RA.

A comprehensive series of sensitivity analyses were conducted to ensure the robustness of our findings. We extended the fully adjusted model by incorporating prevalent diseases at baseline (hypertension, diabetes, CVD,

asthma, chronic obstructive pulmonary disease, anxiety, and depression) and by including CRP as an additional covariate. To address missing data, we reanalyzed the data by treating missing values as a distinct category in the main analyses. To mitigate potential reverse causation, we excluded participants who experienced events within the first two years of follow-up. Given that RA medications, disease activity, and severity may influence complications and mortality post-RA diagnosis but are only available at baseline in the UK Biobank, we were unable to adjust for these factors during follow-up. Therefore, we conducted alternative analyses using prevalent RA at baseline as the exposure when examining RA complications and all-cause mortality outcomes.

All the statistical analyses were conducted using R software version 4.3.1. We used Monte Carlo simulation (parametric bootstrapping) with 10000 runs to calculate the CIs of the life expectancy estimation with the boot R package. All the statistical tests were two-sided, and a *P* value of less than 0.05 was considered to indicate statistical significance.

RESULTS
Baseline characteristics

The baseline characteristics of the included participants are presented in [Table 1](#). Among the 302,239 participants, 3,649 (1.2%) developed incident RA over a median follow-up of 12.5 years. The mean age of the participants was 57.9 years (SD: 6.8 years), and 47.6% were male ([Table 1](#)).

Incident RA

The associations of body size change and SDOHs with incident RA are presented in [Figures 1-3](#), which revealed significant interaction effects (*P* for interaction<0.05). Adverse body size changes, combined with unfavorable SDOHs, were associated with an increased risk of RA. The dose-response relationships between adulthood body size indicators and RA within each childhood body size category are shown in [Figure 4](#). RCS revealed similar patterns across childhood body size groups for all adulthood body size indicators: HRs started slightly below 1, gradually rising until reaching the upper normal range of BMI, WHR, or WHtR, where HR reached 1. Beyond this point,

Table 1. Baseline characteristics of the participants.

	Overall (N=302239)	RA (N=3649)	Non-RA (N=298590)
Age at recruitment, years, mean (SD)	57.9 (6.8)	60.0 (6.4)	57.8 (6.8)
Sex, n (%)			
Female	158307 (52.4%)	2294 (62.9%)	156013 (52.3%)
Male	143932 (47.6%)	1355 (37.1%)	142577 (47.8%)
Region, n (%)			
Urban	279299 (92.4%)	3408 (93.4%)	275891 (92.4%)
Rural	22940 (7.6%)	241 (6.6%)	22699 (7.6%)
Smoking status, n (%)			
Never	162253 (53.7%)	1611 (44.1%)	160642 (53.8%)
Previous	110672 (36.6%)	1564 (42.9%)	109108 (36.5%)
Current	29314 (9.7%)	474 (13.0%)	28840 (9.7%)
Alcohol drinking frequency, n (%)			
>= 3 times/week	141338 (46.8%)	1423 (39.0%)	139915 (46.9%)
< 3 times/week	140421 (46.5%)	1829 (50.1%)	138592 (46.4%)
Never	20480 (6.8%)	397 (10.9%)	20083 (6.7%)
Sleep duration, n (%)			
7-8 h/day	206406 (68.3%)	2170 (59.5%)	204236 (68.4%)
< 7 h/day	73272 (24.2%)	1104 (30.3%)	72168 (24.2%)
> 8 h/day	22561 (7.5%)	375 (10.3%)	22186 (7.4%)

Table 1. (Continued)

	Overall (N=302239)	RA (N=3649)	Non-RA (N=298590)
Healthy diet score, n (%)			
0-2	111380 (36.9%)	1295 (35.5%)	110085 (36.9%)
3-5	179880 (59.5%)	2203 (60.4%)	177677 (59.5%)
>=6	10979 (3.6%)	151 (4.1%)	10828 (3.6%)
Physical activity, n (%)			
High	57283 (19.0%)	794 (21.8%)	56489 (18.9%)
Moderate	123987 (41.0%)	1393 (38.2%)	122594 (41.1%)
Low	120969 (40.0%)	1462 (40.1%)	119507 (40.0%)
Childhood body size, n (%)			
Average	153425 (50.8%)	1707 (46.8%)	151718 (50.8%)
Plumper	48004 (15.9%)	676 (18.5%)	47328 (15.9%)
Thinner	100810 (33.4%)	1266 (34.7%)	99544 (33.3%)
Adulthood BMI, kg/m², mean (SD)			
	27.4 (4.7)	28.8 (5.5)	27.4 (4.7)
Adulthood BMI, n (%)			
Normal	98122 (32.5%)	922 (25.3%)	97200 (32.6%)
Overweight	130759 (43.3%)	1457 (39.9%)	129302 (43.3%)
Obesity	73358 (24.3%)	1270 (34.8%)	72088 (24.1%)
Adulthood WHR, mean (SD)			
	0.876 (0.090)	0.881 (0.091)	0.876 (0.090)
Adulthood WHR, n (%)			
Low WHR	105060 (34.8%)	972 (26.6%)	104088 (34.9%)
Intermediate WHR	95742 (31.7%)	1063 (29.1%)	94679 (31.7%)
High WHR	101437 (33.6%)	1614 (44.2%)	99823 (33.4%)
Adulthood WHtR, mean (SD)			
	0.538 (0.074)	0.560 (0.083)	0.537 (0.074)
Adulthood WHtR, n (%)			
Low WHtR	95012 (31.4%)	852 (23.3%)	94160 (31.5%)
Intermediate WHtR	151239 (50.0%)	1760 (48.2%)	149479 (50.1%)
High WHtR	55988 (18.5%)	1037 (28.4%)	54951 (18.4%)
RA PRS, n (%)			
Low risk	151120 (50.0%)	1472 (40.3%)	149648 (50.1%)
High risk	151119 (50.0%)	2177 (59.7%)	148942 (49.9%)
SDOHs, n (%)			
Unfavorable	132987 (44.0%)	1945 (53.3%)	131042 (43.9%)
Favorable	169252 (56.0%)	1704 (46.7%)	167548 (56.1%)
Death, n (%)			
No	279953 (92.6%)	3186 (87.3%)	276767 (92.7%)
Yes	22286 (7.4%)	463 (12.7%)	21823 (7.3%)

RA, rheumatoid arthritis; PRS, polygenic risk score; BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; SDOHs, social determinants of health; SD: standard deviation.

as BMI, WHR, and WHtR increased further, HRs increased sharply. [Figures S3-S5](#) present the joint associations of body size change and SDOHs with RA, with associations stratified by age and sex.

Age at onset of RA

[Figure 5](#) shows the associations of body size change and SDOHs with age

at onset of RA. For any level of childhood body size, changes ending in a normal BMI, low WHR, or low WHtR group in adulthood generally presented the lowest risk. However, for each childhood body size, changes leading to overweight or obesity for BMI, and to medium or high for WHR/WHtR in adulthood were progressively associated with increased risk. These patterns were evident in both favorable and unfavorable SDOHs, with unfavorable

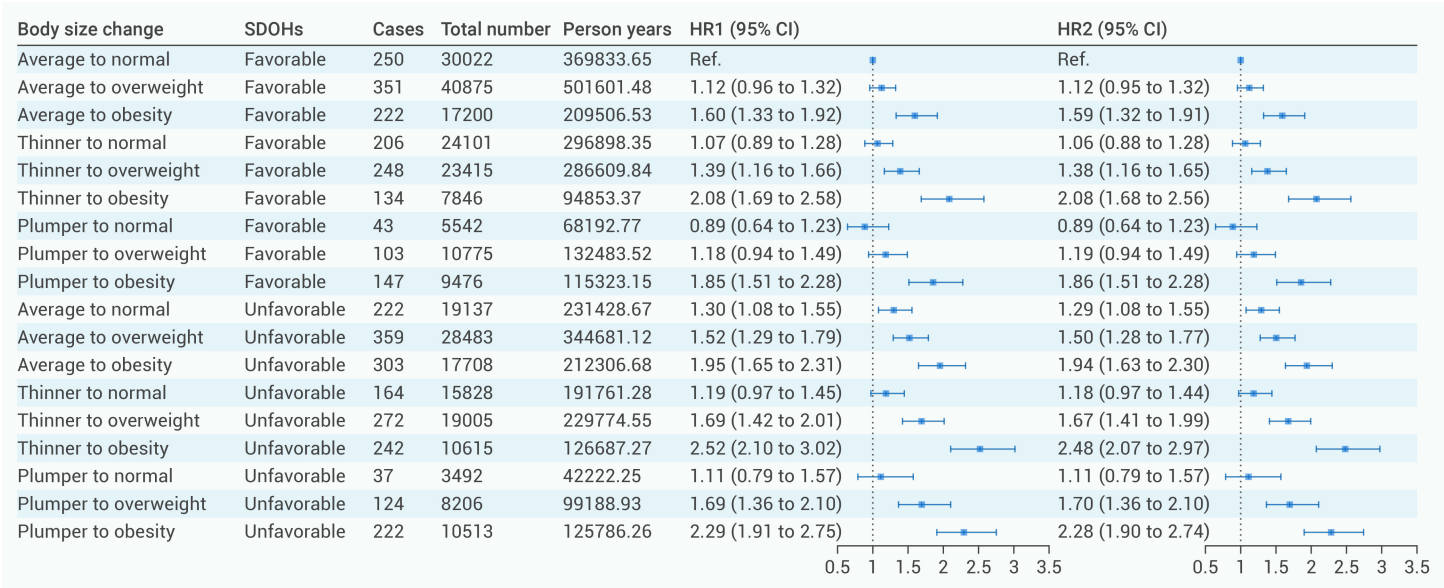


Figure 1. Associations of body size change (compare body size at 10 years-adulthood BMI) and SDOHs with incident RA RA, rheumatoid arthritis; SDOHs, social determinants of health; PRS, polygenic risk score; BMI, body mass index; HR, hazard ratio; CI, confidence interval; Ref., reference. Social determinants were classified into two categories on the basis of the median: "favorable" and "unfavorable". Model 1 was adjusted for age at recruitment, sex, region, smoking status, alcohol consumption frequency, sleep duration, healthy diet score, and physical activity. Model 2 was further adjusted for RA PRS, the genotyping array, and the first 10 principal components of ancestry.

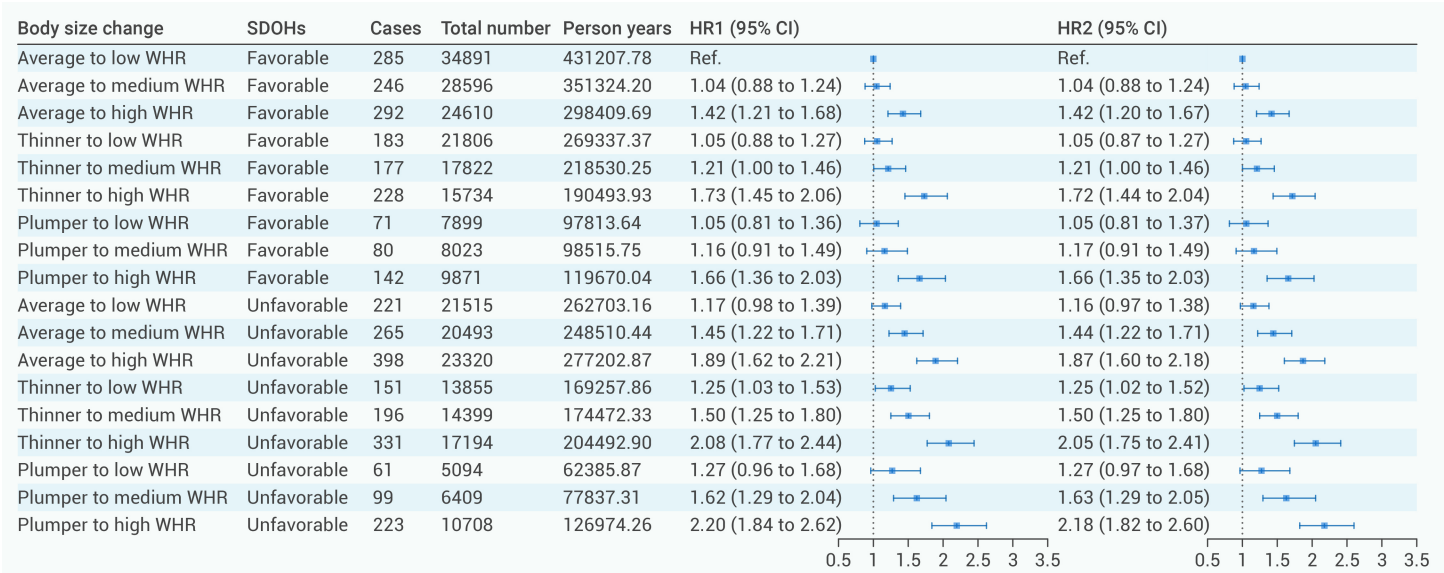


Figure 2. Associations of body size change (compare body size at 10 years-adulthood WHR) and SDOHs with incident RA RA, rheumatoid arthritis; SDOHs, social determinants of health; PRS, polygenic risk score; WHR, waist-to-hip ratio; HR, hazard ratio; CI, confidence interval; Ref., reference. Social determinants were classified into two categories on the basis of the median: "favorable" and "unfavorable". Model 1 was adjusted for age at recruitment, sex, region, smoking status, alcohol consumption frequency, sleep duration, healthy diet score, and physical activity. Model 2 was further adjusted for RA PRS, the genotyping array, and the first 10 principal components of ancestry.

SDOHs exacerbating the risks. A consistent pattern was observed for all three measures (BMI, WHR, and WHtR) and for all age groups, and the combination of adverse body size changes (e.g., ending in obesity for BMI or the highest level for WHR/WHtR) and unfavorable SDOHs presented the highest risk.

Complications after RA diagnosis

Adverse body size changes, particularly those ending in overweight/obesity or abdominal obesity, combined with unfavorable SDOHs were associated with increased risks of multiple complications after RA diagnosis, including CVD, lung disease, CKD, osteoporosis, and anemia (Table 2).

Life expectancy

Figure 6 presents life expectancy differences from age 50 onward by body size change and SDOHs. At the age of 50 years, for the BMI indicator, compared with favorable SDOHs, life expectancy reductions in the unfavor-

able group were 4.1 (95% CI 3.3–4.9) years for men and 1.9 (1.3–2.6) years for women with a thinner/average to normal change, 2.9 (2.2–3.6) years for men and 1.6 (1.1–2.1) years for women with a thinner/average to overweight/obesity change, 2.9 (1.9–3.9) years for men and 1.6 (0.7–2.5) years for women with a plumper to normal change, and 3.0 (2.4–3.6) years for men and 2.6 (1.9–3.2) years for women with a plumper to overweight/obesity change. Similar reductions were observed for WHR: 3.0 (2.2–3.8) years and 1.4 (0.9–2.0) years in the thinner/average to normal change, 3.2 (2.6–3.8) years and 2.1 (1.4–2.7) years in the thinner/average to abdominal obesity change, 2.7 (1.7–3.8) years and 1.6 (0.6–2.7) years in the plumper to normal change, and 3.2 (2.6–3.8) years and 2.8 (2.3–3.3) years in the plumper to abdominal obesity change. For the WHtR, the reductions were 3.5 (2.8–4.2) years and 1.8 (1.2–2.5) years in the thinner/average to normal change, 3.1 (2.5–3.7) years and 1.6 (1.0–2.3) years in the thinner/average to abdominal obesity change, 3.6 (2.5–4.6) years and 2.2 (1.1–3.3) years in the plumper to

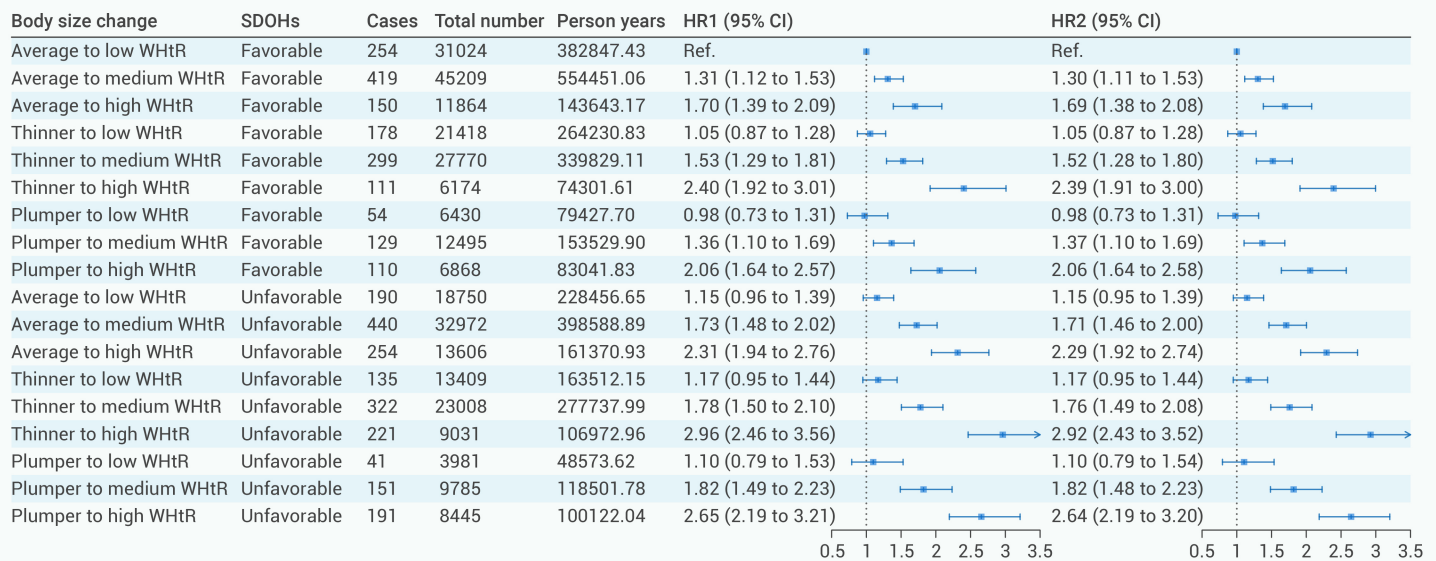


Figure 3. Associations of body size change (compare body size at 10 years-adulthood WHtR) and SDOHs with incident RA RA, rheumatoid arthritis; SDOHs, social determinants of health; PRS, polygenic risk score; WHtR, waist-to-height ratio; HR, hazard ratio; CI, confidence interval; Ref., reference. Social determinants were classified into two categories on the basis of the median: "favorable" and "unfavorable". Model 1 was adjusted for age at recruitment, sex, region, smoking status, alcohol consumption frequency, sleep duration, healthy diet score, and physical activity. Model 2 was further adjusted for RA PRS, the genotyping array, and the first 10 principal components of ancestry.

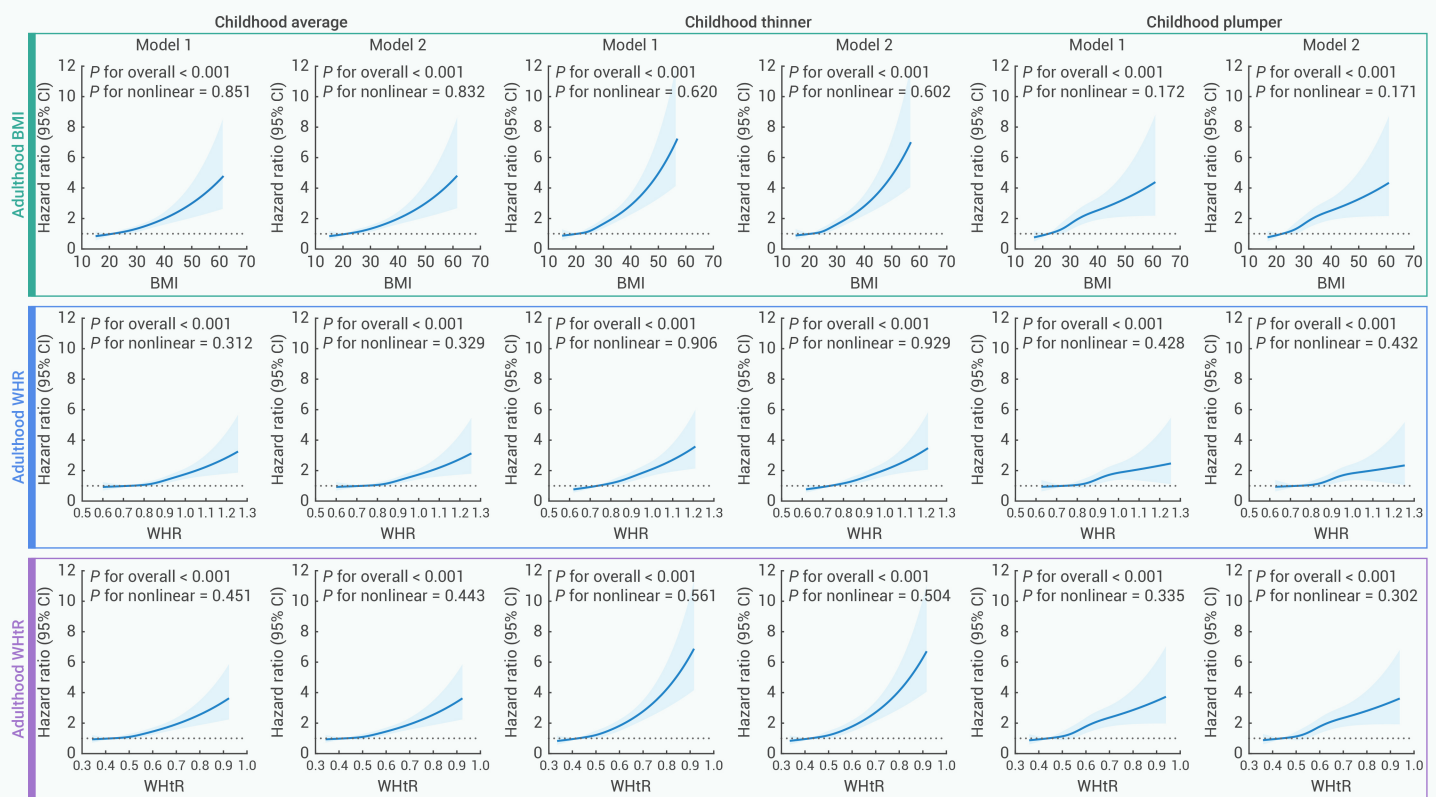


Figure 4. Dose-response relationships between adulthood body size indicators and RA within each childhood body size category RA, rheumatoid arthritis; PRS, polygenic risk score; BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; HR, hazard ratio; CI, confidence interval. Dose-response associations (HR and 95% CI) were examined using restricted cubic splines with four knots located at the 5th, 35th, 65th, and 95th percentiles of each exposure. Model 1 was adjusted for age at recruitment, sex, region, smoking status, alcohol consumption frequency, sleep duration, healthy diet score, and physical activity. Model 2 was further adjusted for RA PRS, the genotyping array, and the first 10 principal components of ancestry.

normal change, and 2.9 (2.2–3.5) years and 2.6 (2.1–3.1) years in the plumper to abdominal obesity change. We further examined differences in estimated life expectancy from age 50 onward on the basis of body size change and RA status (Figure S6) as well as differences in SDOHs and RA status (Figure S7).

Supplement and sensitivity analyses

Tables S5–S6 show independent associations of body size change with incident RA and age at onset. Tables S7–S9 present the combined effects of body size change and SDOHs on all-cause mortality. The multistate analysis of the transitions from RA-free to RA and then to death, considering the joint effects of body size change and SDOHs, is shown in Figure S2 and Table S10.

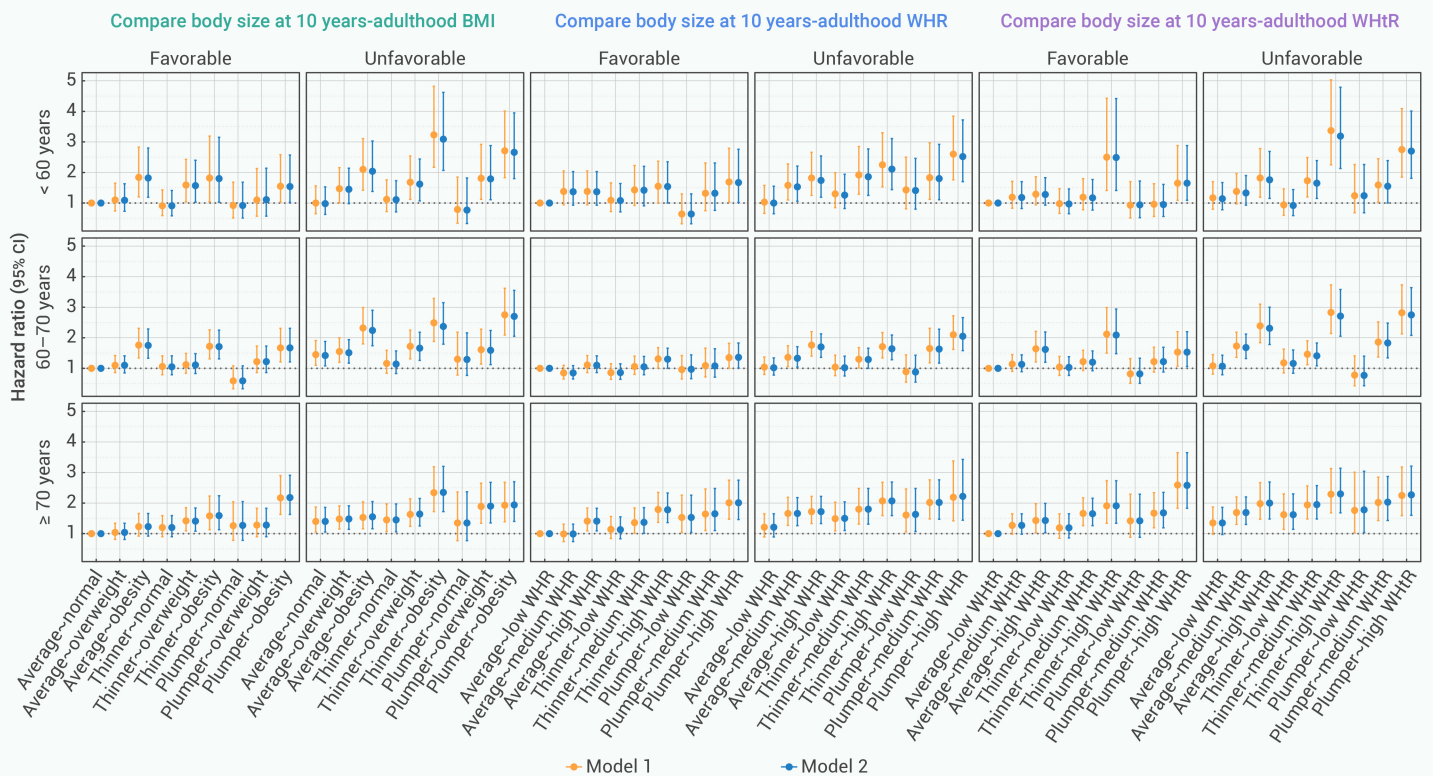


Figure 5. Associations of body size change and SDOHs with age at onset of RA SDOHs, social determinants of health; RA, rheumatoid arthritis; PRS, polygenic risk score; BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; CI, confidence interval. Social determinants were classified into two categories on the basis of the median: "favorable" and "unfavorable". Model 1 was adjusted for sex, region, smoking status, alcohol consumption frequency, sleep duration, healthy diet score, and physical activity. Model 2 was further adjusted for RA PRS, the genotyping array, and the first 10 principal components of ancestry.

Table S11 reports the associations of childhood or adulthood body size with incident RA, and Table S12 presents CRP mediation in associations between body size change, SDOHs, and RA. A significant interaction between body size change and RA PRS, with adverse trajectories plus high RA PRS increasing RA risk, is shown in Tables S13-S15. The results remained robust after adjusting for baseline diseases (Tables S16-S18) or CRP levels (Tables S19-S21) and were only slightly altered when early cases were excluded (Tables S22-S24) or when missing data were treated as a distinct category (Tables S25-S27). The joint associations of body size change and the RA PRS with RA are shown in Tables S28-S30. Alternative analyses using baseline prevalent RA as exposure and complications or mortality as outcomes, accounting for RA medications, disease activity, and severity, are shown in Tables S31-S35.

DISCUSSION

In this large-scale prospective cohort study, we observed that adverse body size changes combined with unfavorable SDOHs are significantly associated with an increased risk of developing RA, age at onset of RA, and complications after RA diagnosis. Notably, significant disparities in estimated life expectancy were observed by the SDOHs; individuals with unfavorable SDOHs experienced shorter life expectancies compared with those with favorable SDOHs across all body size change groups. These findings are crucial for informing health policies and developing effective interventions to address both obesity changes and socioeconomic disparities in the development of RA risk and to prolong life expectancy among middle-aged and older adults.

Previous studies have established that both childhood and adulthood obesity are significant risk factors for RA development.^{6-7,11,39} However, understanding how different aspects of body composition contribute to RA risk requires a more nuanced approach. A key strength of our study was the comprehensive assessment of body size using three measures—BMI, WHR, and WHtR—each of which captures a distinct aspect of adiposity.^{40,41} The innovation of our study lies in the use of childhood-to-adulthood body size changes, which provide a dynamic view of how changes in adiposity over

time influence RA risk. This approach allowed us to go beyond static measurements, offering insight into the long-term effects of weight gain and fat distribution on RA development. We found that changes ending in overweight or obesity, as well as those with medium or high WHR/WHtR in adulthood, progressively increased the risk of RA, whereas changes ending with a normal BMI or low WHR/WHtR in adulthood generally did not show statistically significance, even among individuals who were plumper in childhood. These findings suggest that maintaining a normal weight and healthy fat distribution in adulthood can mitigate RA risk, irrespective of earlier life body size. These findings highlight the critical role of lifestyle interventions, particularly maintaining healthy weight and fat distribution, in reducing RA risk and promoting healthy aging, suggesting that it is never too late to adopt health-behaviors.

While extensive literature exists on the relationships between SDOHs and various diseases, research specifically addressing the association between SDOHs and RA remains limited, often constrained by small sample sizes,^{16,17} a lack of longitudinal data,¹⁸ and a focus on only a few SDOH factors.¹⁹ Our large and prospective study addresses these gaps by adopting a comprehensive approach, incorporating 20 distinct SDOHs items across five key domains to provide a multidimensional perspective on how various social, economic, and environmental factors collectively impact RA risk. Additionally, while previous studies have focused primarily on the incidence of RA, we expanded our analysis to include the age at onset, providing new insights into the timing of RA development. Consequently, our study provides high-quality evidence on the association between SDOHs and RA, highlighting the importance of addressing these social factors early in life to delay or prevent RA onset, particularly in socially disadvantaged groups.

Adverse body size changes, particularly central obesity, initiate a cascade of events leading to RA, its complications, and ultimately increased mortality risk. Central obesity induces chronic low-grade inflammation by releasing proinflammatory cytokines from adipose tissue, disrupting immune regulation and promoting autoimmunity.^{42,43} This process is exacerbated by unfavorable SDOHs, which aggravates this inflammatory state, further increasing RA risk by delaying diagnosis and treatment. Once RA is established,

Table 2. Associations of body size change and SDOHs with complications after RA diagnosis.

Body size change	SDOHs	CVD	Lung disease	CKD	Osteoporosis	Anemia
		N=183736	N=281190	N=275838	N=252057	N=273338
		HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Compare body size at 10 years-adulthood BMI						
Thinner/Average to normal	Favorable	Ref.	Ref.	Ref.	Ref.	Ref.
Thinner/Average to overweight/obesity	Favorable	1.43 (1.01-2.02)	1.22 (0.71-2.08)	1.89 (1.17-3.03)	1.57 (1.05-2.33)	1.79 (1.13-2.86)
Plumper to normal	Favorable	0.67 (0.21-2.15)	1.16 (0.54-2.77)	1.91 (0.66-5.55)	1.51 (0.59-3.87)	1.80 (0.62-5.21)
Plumper to overweight/obesity	Favorable	2.09 (1.34-3.28)	1.72 (1.01-3.06)	3.60 (2.08-6.23)	2.15 (1.29-3.59)	2.79 (1.59-4.89)
Thinner/Average to normal	Unfavorable	1.62 (1.07-2.43)	1.77 (1.00-3.21)	2.09 (1.21-3.58)	1.37 (0.84-2.23)	2.23 (1.32-3.77)
Thinner/Average to overweight/obesity	Unfavorable	2.54 (1.81-3.56)	2.42 (1.46-4.01)	3.77 (2.39-5.95)	2.05 (1.38-3.06)	2.97 (1.89-4.67)
Plumper to normal	Unfavorable	1.67 (0.66-4.23)	1.93 (0.57-6.54)	2.48 (0.85-7.23)	1.35 (0.41-4.41)	2.45 (0.84-7.11)
Plumper to overweight/obesity	Unfavorable	2.30 (1.46-3.64)	2.39 (1.27-4.49)	3.94 (2.28-6.78)	3.12 (1.93-5.03)	3.36 (1.95-5.79)
Compare body size at 10 years-adulthood WHR						
Thinner/Average to normal	Favorable	Ref.	Ref.	Ref.	Ref.	Ref.
Thinner/Average to abdominal obesity	Favorable	1.32 (1.02-1.79)	1.24 (0.87-1.78)	1.93 (1.27-2.93)	1.24 (0.87-1.78)	1.37 (0.92-2.04)
Plumper to normal	Favorable	0.87 (0.45-1.68)	1.19 (0.50-2.86)	2.23 (1.13-4.41)	1.56 (0.85-2.86)	1.72 (0.88-3.34)
Plumper to abdominal obesity	Favorable	2.03 (1.30-3.17)	1.75 (1.03-2.82)	3.68 (2.17-6.23)	1.75 (1.02-2.97)	2.25 (1.31-3.88)
Thinner/Average to normal	Unfavorable	1.37 (1.00-1.90)	1.45 (0.90-2.33)	2.50 (1.63-3.84)	1.29 (0.88-1.90)	1.52 (1.00-2.31)
Thinner/Average to abdominal obesity	Unfavorable	2.31 (1.73-3.09)	2.12 (1.39-3.24)	3.47 (2.34-5.16)	1.69 (1.20-2.40)	2.62 (1.82-3.77)
Plumper to normal	Unfavorable	1.20 (0.62-2.33)	1.54 (0.68-3.51)	2.17 (1.03-4.55)	1.86 (1.00-3.48)	1.71 (0.83-3.52)
Plumper to abdominal obesity	Unfavorable	2.26 (1.45-3.52)	2.13 (1.17-3.87)	4.25 (2.56-7.05)	2.63 (1.65-4.20)	2.99 (1.83-4.89)
Compare body size at 10 years-adulthood WHtR						
Thinner/Average to normal	Favorable	Ref.	Ref.	Ref.	Ref.	Ref.
Thinner/Average to abdominal obesity	Favorable	1.37 (1.03-1.88)	1.37 (0.84-2.23)	2.57 (1.48-4.45)	1.89 (1.23-2.90)	1.65 (1.03-2.65)
Plumper to normal	Favorable	0.77 (0.50-1.66)	1.02 (0.60-1.75)	1.72 (0.50-5.95)	1.26 (0.44-3.61)	1.16 (0.35-3.87)
Plumper to abdominal obesity	Favorable	2.05 (1.32-3.20)	1.70 (1.00-2.88)	4.99 (2.70-9.23)	2.68 (1.57-4.58)	2.81 (1.60-4.95)
Thinner/Average to normal	Unfavorable	1.24 (0.80-1.94)	1.53 (0.82-2.85)	2.32 (1.21-4.44)	1.08 (0.60-1.95)	1.72 (0.97-3.06)
Thinner/Average to abdominal obesity	Unfavorable	2.40 (1.71-3.36)	2.12 (1.28-3.51)	4.99 (2.91-8.53)	2.56 (1.67-3.93)	2.92 (1.84-4.62)
Plumper to normal	Unfavorable	1.46 (0.58-3.69)	1.67 (0.49-5.69)	3.19 (1.06-9.64)	1.92 (0.67-5.50)	2.22 (0.76-6.46)
Plumper to abdominal obesity	Unfavorable	2.15 (1.36-3.40)	2.12 (1.13-3.99)	5.20 (2.81-9.62)	3.60 (2.16-6.00)	3.22 (1.85-5.59)

RA, rheumatoid arthritis; SDOHs, social determinants of health; PRS, polygenic risk score; CVD, cardiovascular disease; CKD, chronic kidney disease; BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; HR, hazard ratio; CI, confidence interval; Ref., reference. SDOHs were classified into two categories on the basis of the median: "favorable" and "unfavorable". For each complication, we excluded prevalent cases at baseline and further excluded cases where complications occurred without a prior RA diagnosis or developed before or concurrent with RA. The model was adjusted for age at recruitment, sex, region, smoking status, alcohol consumption frequency, sleep duration, healthy diet score, physical activity, RA PRS, genotyping array, and the first 10 principal components of ancestry.

systemic inflammation extends beyond the joints: it impairs atherosclerosis and endothelial dysfunction, leading to CVD; affects lung tissue, causing interstitial lung disease; damages kidney function, potentially triggering chronic kidney disease; accelerates bone resorption and decreased formation, resulting in osteoporosis; and suppresses erythropoiesis while altering iron metabolism, causing anemia.^{20,44-47} These complications form a vicious cycle, exacerbating RA symptoms, while RA itself worsens complications, collectively increasing mortality risk.

To our knowledge, this is the first study to estimate life expectancy by jointly considering body size changes and SDOH. We observed that unfavorable SDOH associated with the shortest life expectancy across all body size changes, suggesting that physical health factors alone cannot address public

health challenges, and broader structural and environmental factors are crucial in shaping life expectancy disparities. Notably, our life expectancy analysis highlighted two distinct inequalities. First, unfavorable SDOHs is consistently associated with shorter life expectancy across all body size change groups, with these effects being more pronounced in men. This gender disparity likely reflects societal constructs: men with unfavorable SDOHs might face compound pressures to engage in high-risk occupations or delay healthcare-seeking behaviors due to cultural norms, exacerbating the biological consequences of body size changes.^{48,49} Second, RA itself substantially reduces life expectancy across SDOHs and body size groups but has greater effects on women. This may reflect a longer disease duration, greater systemic inflammation, or undertreatment in women, compounded

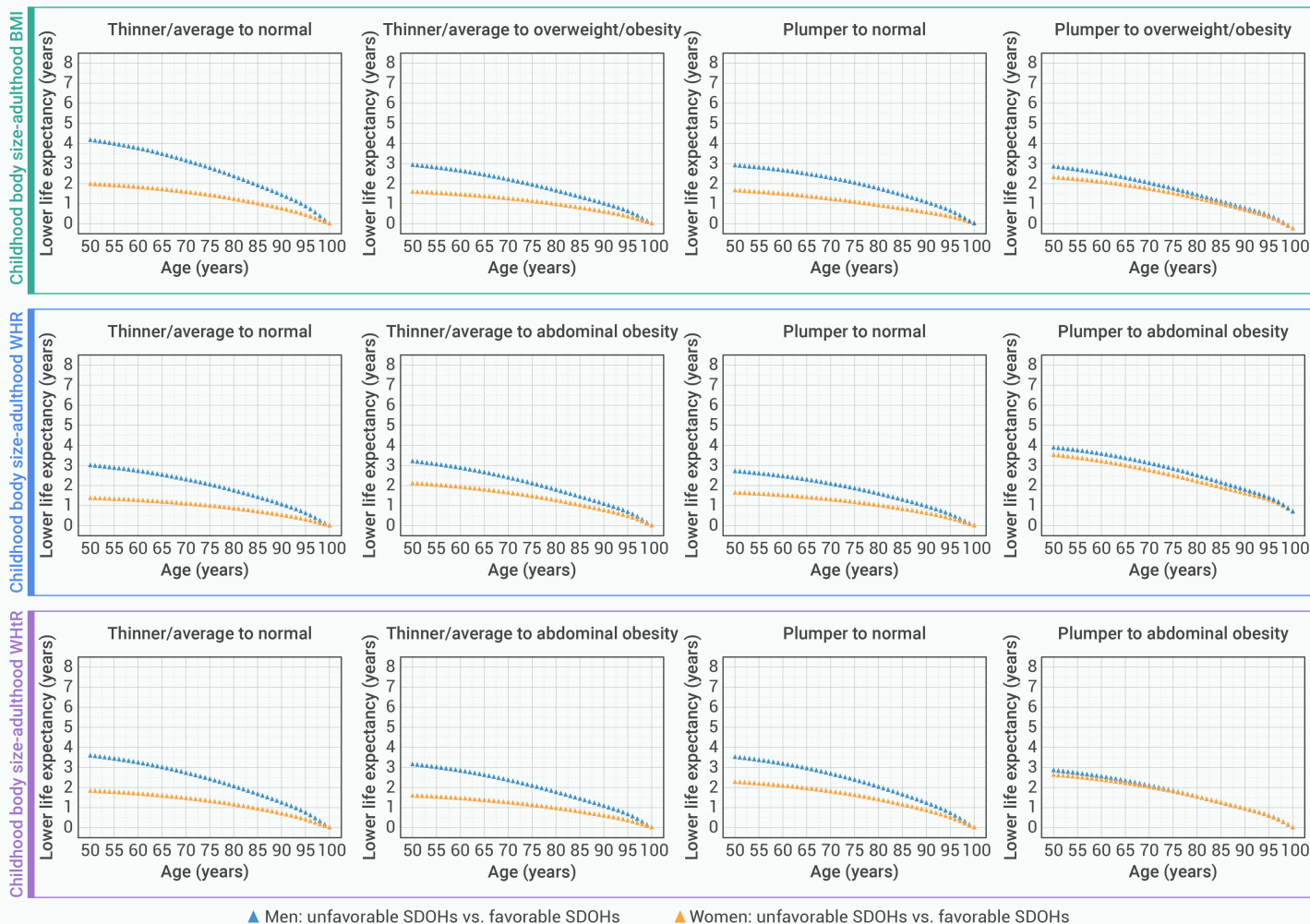


Figure 6. Differences in estimated life expectancy from 50 years of age onward by body size change and SDOHs SDOHs, social determinants of health; BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio. SDOHs were classified into two categories on the basis of the median: "favorable" and "unfavorable". A lower life expectancy was calculated by comparing the estimated life expectancy of individuals in the favorable group with that of those in the unfavorable group. The model was adjusted for age at recruitment, sex, region, smoking status, alcohol consumption frequency, sleep duration, healthy diet score, and physical activity.

by socioeconomic strain and caregiving roles.^{50,51} Our findings underscore how the burden of premature mortality is unequally distributed across social and biological axes, with differing manifestations in men and women. These results reveal underrecognized mortality burdens and offer actionable insights for risk stratification, targeted interventions, and long-term survivorship planning in RA care.

These findings have important implications for clinical care and public health policy. First, the consistent impact of adverse SDOHs across all body size change groups highlights the urgent need to improve equitable access to rheumatology services for socially disadvantaged populations, reducing delays that exacerbate RA and its associated complication risks and improving life expectancy. Second, the observed synergistic effects of early-life body size and adult adiposity suggest that obesity prevention and healthy growth trajectory interventions should begin in childhood and continue through adulthood, particularly in socioeconomically vulnerable groups. These could include school-based nutrition and physical activity programs, community-led lifestyle coaching, and longitudinal support in primary care.⁵² Third, our findings support the integration of SDOHs screening tools and body size change assessments into RA risk stratification models, enabling clinicians and health systems to identify high-risk individuals. Together, these strategies align with precision prevention and health equity frameworks and underscore the need to address upstream social and metabolic risks to reduce the RA burden and narrow disparities in long-term outcomes.

Several limitations should be acknowledged. First, self-reported childhood body size may introduce recall bias, although a meta-analysis involving over

122,000 children revealed strong agreement between self-reported and measured values.⁵³ Moreover, this self-reported childhood body size measure has been widely adopted in other UK Biobank studies,^{10,25,54} supporting its utility in large-scale epidemiological research. Second, we lack repeated body size measurements for both childhood and adulthood, preventing us from capturing weight fluctuations over time. Additionally, we lack childhood socioeconomic data, preventing us from analyzing how changes in socioeconomic status might differentially affect weight in childhood versus adulthood.⁵⁵ The absence of data on childhood lifestyles, such as diet and physical activity, and their changes into adulthood may introduce residual confounding factors.¹⁰ Third, information on SDOHs and covariates was collected only once at baseline, failing to capture changes over time. Fourth, although we controlled for major confounders, the potential for residual confounding to bias our results remains. However, sensitivity analyses support the robustness of our findings. Fifth, while we considered different contributions of the SDOHs, our scoring method may not fully capture the complex interactions among these determinants. There is a need for a well-recognized method to better evaluate the cumulative effects of SDOHs. Additionally, while our study incorporates both individual-level and area-level SDOHs, the use of area-level metrics (e.g., IMD scores) may introduce an ecological fallacy. Sixth, our inability to adjust for RA medications, disease activity, and severity during follow-up, as these data were only available at baseline, limits the understanding of their impact on RA complications. Additionally, this study is limited by the lack of data on treatment efficacy, treatment adherence, and delayed diagnosis. This prevents us from conducting

further analyses, such as evaluating whether disadvantaged groups exhibit poorer treatment responses, which would strengthen the clinical relevance of the findings. Finally, the UK Biobank is not a nationally representative cohort, and healthy volunteer selection bias has been discussed previously, which may underestimate risks in socioeconomically disadvantaged populations.⁵⁶ External validation with more representative cohorts and targeted recruitment for underrepresented groups would be valuable to confirm our findings across different socioeconomic strata.

In conclusion, our study highlights that the combined effects of adverse body size changes and unfavorable SDOHs are significantly associated with an increased risk of incident and age at onset of RA, complications after RA diagnosis, and reduced life expectancy. These results underscore the critical need for public health strategies addressing both individual-level factors and broader structural determinants to effectively reduce the RA burden and promote healthy aging.

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AUTHOR CONTRIBUTIONS

YY, WC, and YL contributed to the development of the study concept and design. YY cleaned the data, performed the statistical analyses, and wrote the first draft of the study. All the authors revised the manuscript. YL and WC obtained the funding and were responsible for the decision to submit the manuscript. All the authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

All participants provided informed consent through electronic signatures at the baseline assessment, and the UK Biobank study was approved by the North West-Haydock Research Ethics Committee (reference 21/NW/0157).

DATA AND CODE AVAILABILITY

The dataset supporting the conclusions of this article is available on the website: <https://www.ukbiobank.ac.uk/>. Access to the UK Biobank resource can be obtained via an approved application.

SUPPLEMENTAL INFORMATION

It can be found online at <https://doi.org/10.59717/j.xinn-med.2025.100134>