ORIGINAL ARTICLE
Overweight across the life course and adipokines, inflammatory and endothelial markers at age 60–64 years: evidence from the 1946 birth cohort

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BACKGROUND/OBJECTIVES: There is growing evidence that early development of obesity increases cardiovascular risk later in life, but less is known about whether there are effects of long-term excess body weight on the biological drivers associated with the atherosclerotic pathway, particularly adipokines, inflammatory and endothelial markers. This paper therefore investigates the influence of overweight across the life course on levels of these markers at retirement age.

SUBJECTS/METHODS: Data from the Medical Research Council National Survey of Health and Development (n = 1784) were used to examine the associations between overweight status at 2, 4, 6, 7, 11, 15, 20, 26, 36, 43, 53 and 60–64 years (body mass index (BMI) ≥ 25 kg m⁻²) and measurements of adipokines (leptin and adiponectin), inflammatory markers (C-reactive protein (CRP), interleukin-6 (IL-6)) and endothelial markers (E-selectin, tissue plasminogen activator (t-PA) and von Willebrand factor) at 60–64 years. In addition, the fit of different life course models (sensitive periods/accumulation) were compared using partial F-tests.

RESULTS: In age- and sex-adjusted models, overweight at 11 years and onwards was associated with higher leptin, CRP and IL-6 and lower adiponectin; overweight at 15 years and onwards was associated with higher E-selectin and t-PA. Associations between overweight at all ages earlier than 60–64 with leptin, adiponectin, CRP and IL-6 were reduced but remained apparent after adjustment for overweight at 60–64 years; whereas those with E-selectin and t-PA were entirely explained. An accumulation model best described the associations between overweight across the life course with adipokines and inflammatory markers, whereas for the endothelial markers, the sensitive period model for 60–64 years provided a slightly better fit than the accumulation model.

CONCLUSIONS: Overweight across the life course has a cumulative influence on adipokines, inflammatory and possibly endothelial markers. Avoidance of overweight from adolescence onwards is likely important for cardiovascular disease prevention.

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INTRODUCTION
Overweight and obesity represent a major global health problem; the World Health Organization estimated that in 2008, more than 1.4 billion adults were overweight (body mass index (BMI) 25–29 kg m⁻²) and 500 million obese (BMI ≥ 30 kg m⁻²) globally.¹ It has been calculated that if all persons were not overweight or obese, ~ 3.4 million (6.4%) of all deaths annually,² and approximately a quarter of all deaths due to ischaemic heart disease could be prevented;³ the largest single cause of death.³

In recent years, the mechanism(s) by which excess body weight produces adverse cardiovascular outcomes has attracted interest, with one potential pathway being the dysfunction of adipose tissue.⁴,⁵ When energy balance is positive, more calories are consumed than expended, adipocytes fill up with fatty acids, and patterns of adipokine secretion are altered; leptin secretion rises and adiponectin declines. The rising concentration of leptin is known about whether there are persistent effects of long-term excess body weight on the biological drivers associated with the atherosclerotic pathway, particularly adipokines, inflammatory and endothelial markers, which have collectively been referred to as ‘adiposopathic markers’⁷ because their secretion is associated with adipose tissue hypertrophy. Numerous studies have documented cross-sectional associations between higher levels of adiposity and adverse levels of these ‘adiposopathic’ markers, in mid to late adulthood,¹²,¹³ with relatively short-term changes in weight altering the levels of these factors.¹⁴–¹⁸ A few studies have shown that weight gain from adolescence to young adulthood, and from early to mid-adulthood, are associated with higher levels of inflammatory marker C-reactive protein (CRP) at ages 18, (ref.19) 22 (ref.20) and 31 years.²¹ However, it is not clear how much adiposity levels before middle age affect levels of adiposopathic

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markers in later life, and whether any influence reflects a cumulative process or the influence of adiposity at specific sensitive periods. If it can also be shown that levels of other inflammatory markers, plus adipokines and endothelial markers, are associated with excess body weight at similar ages in the life course, this would give additional support to the hypothesis that adipose tissue dysfunction is one of the pathways by which overweight and obesity lead to cardiovascular disease (CVD).

We have therefore used data from the Medical Research Council National Survey of Health and Development (NSHD) to explore at what stage in the life course overweight is associated with adiposopathic markers of adipokines (leptin and adiponectin), inflammatory (CRP, interleukin-6 (IL-6) and endothelial markers (E-selectin, tissue plasminogen activator (t-PA) and von Willebrand factor (vWF)) measured in early old age (60–64 years). Our aims were to: (1) determine how early in the life course being overweight is associated with each adiposopathic marker; (2) identify whether being overweight at a particular age, or at multiple ages (particularly including adolescence, early adult and later adult), best describes the relationship between overweight across life and each adiposopathic marker; and (3) given the findings of aim 2, whether associations of the chosen model are independent of potential confounders of smoking, childhood social class and adult social class. We have treated overweight as a dichotomous variable, to facilitate the life course analytic approach used in this paper, and to define the specific impact of overweight as commonly defined (BMI \(\geq 25\) kg m\(^{-2}\)).

**MATERIALS AND METHODS**

**Study design**

The Medical Research Council NSHD is a socially stratified British cohort of individuals who have been followed up 23 times between birth and late middle age.\(^{23}\) The original cohort comprised 3362 singleton children born during 1 week in March 1946. At the most recent clinic assessment at 60–64 years (2006–2010), eligible cohort members (those known to be alive and with a known address in England, Scotland or Wales) were invited for an assessment at one of the six clinical research facilities (CRFs) or to be visited by a research nurse at home. Invitations were not sent to those who had died \((n = 778, 14.5\%\) of the original cohort), who had emigrated \((570, 10.6\%\), who were lost to follow-up \((594, 11.1\%\) and who had previously withdrawn from the study \((564, 10.5\%\). Of the 2856 cohort members invited, 1690 \((59.2\%\) attended a CRF for full examination and 539 \((18.9\%\) were examined at home by a trained nurse.\(^{21}\) Ethical approval for the study \((E\text{-selectin, tissue plasminogen activator (t-PA) and von Willebrand factor (vWF)}\) measured in early old age (60–64 years). Our aims were to: (1) determine how early in the life course being overweight is associated with each adiposopathic marker; (2) identify whether being overweight at a particular age, or at multiple ages (particularly including adolescence, early adult and later adult), best describes the relationship between overweight across life and each adiposopathic marker; and (3) given the findings of aim 2, whether associations of the chosen model are independent of potential confounders of smoking, childhood social class and adult social class. We have treated overweight as a dichotomous variable, to facilitate the life course analytic approach used in this paper, and to define the specific impact of overweight as commonly defined (BMI \(\geq 25\) kg m\(^{-2}\)).

**Covariates**

Information on smoking status, occupational social class and disease conditions were obtained by questionnaire at 60–64 years; cigarette smoking was classified into three categories: never, former and current. Father’s occupation when the cohort member was age 4 years and own occupational class at age 53 years were chosen to represent childhood and adult socioeconomic positions, respectively. The Registrar General’s six-group classification\(^{24}\) was collapsed into four groups: professional and intermediate (I and II); skilled non-manual (IIIm); skilled manual (Illm); and semiskilled and unskilled manual (IV and V). Wherever possible, missing values were imputed from adjacent ages \((33\) values from age 11 and 14 values from age 15 for childhood social class; \(107\) values from age 36 for early adulthood; \(107\) values from age 43 for late adulthood). Stroke and CVD diagnoses (angina or myocardial infarction) were based on participant responses indicating at age 53 or 60–64 years whether a doctor had ever diagnosed them with the condition.\(^{26}\)

**Statistical analysis**

Analyses were undertaken using STATA version 12 (STATA corp LP, TX, USA). All adipokines, endothelial and inflammatory markers were positively skewed and therefore transformed using the natural logarithm to achieve normality of their distributions. This analysis comprises three parts aimed at investigating when in the life course excessive body weight may explain differences in the adiposipathic markers examined at the age of 60–64 years. First, age-adjusted models were fitted for each novel risk factor linearly regressed on BMI at each age \((2, 4, 6, 7, 11, 15, 20, 26, 36, 43, 53\) and 60–64 years) separately. Linearity of associations was assessed using scatterplots and Lowess smoothed curves. The same models were then fitted using dichotomised ‘overweight’ and ‘normal weight’ categories using established, worldwide definitions at each age. This dichotomous approach also facilitated the fitting of life course models, as described below. Each natural logarithm-transformed coefficient was multiplied by 100 to express all regression coefficients as mean percentage differences\(^{27}\) in each adiposopathic marker for overweight compared with non-overweight cohort members. Gender differences in the relationships between overweight at each age and each adiposopathic marker were investigated by testing interactions between overweight and each adiposipathic marker. The basic premise of the approach is to compare the model fit of a set of nested life course models with a saturated model containing all possible main effects and interactions. The original paper proposed the use of the F-test to compare the fit of each reduced model with the saturated model. A P-value that was not statistically significant \((P > 0.05)\) indicates that there is no evidence that the more complex model explained the data better than the simpler life course model. We also assessed model fit using Akaike Information Criteria (AIC), where a smaller AIC indicated a better model fit. To avoid zero cell counts in trajectory groups, and to reduce potential multi-collinearity of repeated overweight measurements (Supplementary Table S2), overweight categories at three ages were chosen to represent adolescence \((15\) years), mid-adulthood \((36\) years) and early adult age \((60–64\) years) for this section of the analyses; resulting in eight possible trajectories. We did not include overweight status for childhood ages in life course models, as the prevalence of overweight before puberty was low in this cohort. In the main analysis, the life course models analysed were as follows: (1) sensitive period models for adolescence, mid-adulthood or early old age; and (2) accumulation of risk models of overweight in adolescence and mid-adulthood only, mid-adulthood and early old age only, and across all the three time periods. The three age accumulation models were then split further into a ‘relaxed’ accumulation model where associations of overweight at each age can have different strengths, whereas a ‘strict’ accumulation model indicated strengths of association were equal for all three ages. When there was evidence that two or more life course models for a given outcome provided as good a fit as the saturated model, we selected the model with
the lowest AIC. When the null model fitted the data as well as the saturated model, the null model was selected. Sensitivity analysis was conducted separately replacing overweight at 15 with 20 years, age 36 with 26 or 43 years and age 60–64 with 53 years.

For the third part of the analyses, the best fitting life course model with adjustment for sex and age (in months) were then subsequently adjusted for smoking, and childhood and adulthood socioeconomic positions. To assess whether associations could be explained by disease status, all models were re-run after separate exclusion of prevalent CVD cases (n = 151) and CRP levels indicative of acute infection (>10 mg l−1; n = 107) at age 60–64 years. To investigate bias due to missing data, the main analysis was repeated with added imputed values from 50 imputed datasets obtained via chained equations, using 10 cycles per data set. Analysis was repeated with added imputed values from 50 imputed datasets obtained via chained equations, using 10 cycles per data set.

**RESULTS**

Of the 2229 participants with a clinic or home visit at 60–64 years, 1784 (80.0%) had complete measurements for all seven adiposopathic markers. Those included were slightly younger in age at the time of assessment (63.2 vs 64.0 years), more likely to have attended the clinic than had a home visit (87.3% vs 29.7%), more time of assessment (63.2 vs 64.0 years), more likely to have a stroke at age 60 (26.0% vs 23.1%) and CRP levels indicative of acute infection (12.7% (2.5–24.0%)). vWF was only associated with overweight at the age of 6 years, but not at later ages. The associations between overweight earlier than 60–64 years with leptin, adiponectin, CRP and IL-6 were reduced but remained apparent after adjustment for overweight at age 60–64 years; whereas E-selectin and t-PA were entirely explained. Results using BMI modelled as a continuous measure and those using the cut-off for overweight found similar associations, with the exception that associations of BMI and vWF were apparent at some adult ages when BMI was modelled.

### Table 1. Description of study members in the 1946 British Birth cohort with complete data on adiposopathic markers at age 60–64 years

|                  | Total | N Mean (s.d.) | Total | Men Mean (s.d.) | Total | Women Mean (s.d.) | P-value sex difference |
|------------------|-------|---------------|-------|-----------------|-------|-------------------|------------------------|
| **Mean age (years)** | 1777  | 63.2 (1.1)    | 868   | 63.1 (1.2)      | 909   | 63.2 (1.1)        | 0.14                   |
| **Mean adiponectin (µg ml−1)** | 1784  | 2.5 (0.7)     | 873   | 2.2 (0.7)       | 911   | 2.8 (0.6)         | <0.01                  |
| **Mean leptin (ng ml−1)** | 1784  | 2.5 (0.9)     | 873   | 2.0 (0.8)       | 911   | 3.0 (0.8)         | <0.01                  |
| **Mean E-selectin (ng ml−1)** | 1784  | 3.6 (0.5)     | 873   | 3.6 (0.5)       | 911   | 3.5 (0.4)         | <0.01                  |
| **Mean t-PA (ng ml−1)** | 1784  | 2.1 (0.6)     | 873   | 2.2 (0.6)       | 911   | 2.1 (0.6)         | <0.01                  |
| **Mean vWF (IU ml−1)** | 1784  | 4.8 (0.5)     | 873   | 4.8 (0.5)       | 911   | 4.8 (0.5)         | <0.01                  |
| **Mean CRP (mg l−1)** | 1784  | 0.8 (0.9)     | 872   | 0.8 (0.9)       | 909   | 0.9 (0.9)         | 0.12                   |
| **Mean IL-6 (pg ml−1)** | 1784  | 0.7 (0.7)     | 873   | 0.7 (0.7)       | 911   | 0.7 (0.7)         | 0.05                   |

**Overweight (obese, years), n (%)**

|                  | N  | Mean (s.d.) | N  | Mean (s.d.) | N  | Mean (s.d.) | P-value sex difference |
|------------------|----|-------------|----|-------------|----|-------------|------------------------|
| **2**            | 1397 | 35.2 (15.2) | 692 | 33.8 (16.5) | 705 | 36.5 (13.9) | 0.3                     |
| **4**            | 1551 | 20.3 (5.5)  | 762 | 20.7 (6.7)  | 789 | 19.8 (4.4)  | 0.64                    |
| **6**            | 1461 | 10.5 (0.8)  | 719 | 9.7 (0.6)   | 742 | 11.3 (1.1)  | 0.32                    |
| **7**            | 1502 | 7.5 (0.8)   | 738 | 5.6 (0.3)   | 764 | 9.3 (0.8)   | 0.01                    |
| **11**           | 1508 | 8.0 (0.8)   | 741 | 6.6 (0.7)   | 767 | 9.3 (0.9)   | 0.06                    |
| **15**           | 1384 | 8.6 (0.6)   | 683 | 6.9 (0.4)   | 701 | 10.3 (0.7)  | 0.03                    |
| **20**           | 1464 | 11.7 (1.0)  | 701 | 13.1 (0.4)  | 763 | 10.4 (1.6)  | 0.1                     |
| **26**           | 1567 | 18.0 (1.8)  | 759 | 23.1 (2.0)  | 808 | 13.2 (1.6)  | <0.01                  |
| **36**           | 1624 | 31.2 (4.3)  | 792 | 40.9 (3.9)  | 832 | 21.9 (4.6)  | <0.01                  |
| **43**           | 1677 | 44.3 (9.6)  | 819 | 52.8 (8.6)  | 310 | 36.1 (10.6) | <0.01                  |
| **53**           | 1701 | 65 (20.9)   | 823 | 71.2 (19.7) | 878 | 59.3 (22.0) | <0.01                  |
| **60–64**        | 1781 | 69.5 (27.5) | 873 | 73.9 (26.6) | 910 | 65.3 (28.4) | <0.01                  |

**CVD (%)**

|                  | N  | Mean (s.d.) | N  | Mean (s.d.) | N  | Mean (s.d.) | P-value sex difference |
|------------------|----|-------------|----|-------------|----|-------------|------------------------|
| **1711**         | 8.8 | 828         | 833 | 11.5        | 0.63 | <0.01 |
| **1634**         | 10.8 | 796         | 836 | 10.3        | 0.50 | <0.01 |
| **1634**         | 41.1 | 796         | 838 | 48.1        | 0.34 | <0.01 |
| **1699**         | 53   | 835         | 864 | 53.5        | 0.52 | <0.01 |
| **1699**         | 27.4 | 866         | 908 | 32          | 0.23 | <0.01 |

**Abbreviations:** ASEP, adult socioeconomic position; BMI, body mass index; CRP, C-reactive protein; CSEP, childhood socioeconomic position; CVD, cardiovascular disease; IL-6, interleukin-6; t-PA, tissue plasminogen activator; vWF, von Willebrand factor. *Geometric mean. **Overweight = BMI ≥ 25 kg m−2. 

obese = BMI ≥ 30 kg m−2.
as a continuous variable but not as a dichotomised variable (Supplementary Table S3).

Estimates using the alternative BMI cut-off of 27.5 kg m\(^{-2}\) were higher, but confidence intervals were wider (Supplementary Table S5). With the exception of vWF, models for ages 43, 53 and 60–64 years refitted as three categories of BMI, showed that relationships were dose related with both overweight and obese groups having mean adiponectin, leptin, CRP, IL-6, E-selectin and t-PA values worse than normal weight participants, but with effects stronger for obese participants (Supplementary Table S6).

Interaction tests were also carried out to examine whether the associations between being overweight at any age and adiposopathic markers differed by gender (Supplementary Table S7). There was some evidence that the associations between overweight at adult ages and inflammatory markers (CRP and IL-6) varied by gender, though no other adiposopathic markers showed consistent gender interaction. The main results were therefore presented for both genders combined. Gender-specific analyses of the associations between overweight at each age, fitted separately, and CRP and IL-6 indicated that the pattern of relationships was apparent for both genders but stronger in women; among whom independent associations between BMI in early adult life and adiposopathic markers were observed even after adjustment for BMI at 63 years (Supplementary Table S8).

In order to compare the fit of the different life course models, the sample was restricted further to participants who had BMI measurements at three specific age points, chosen to represent adolescence (15 years), early adulthood (36 years) and early old age (60–64 years; \(n = 1280, 71.7\%\)). Associations of overweight at each age with adiposopathic markers were almost identical, and interpretations unchanged, in the reduced sample (data not shown). Over the three ages, a total of 354 (27.7\%) of participants were never overweight and 323 (25.5\%) were only overweight at age 60–64 years. Among 537 (42.0\%) study members who first became overweight at age 15 or 36 years \((n = 537), 474 (88.2\%)\) subsequently remained overweight.

With adjustments for age and sex, the model where risk accumulated across all three life periods stood out as the best model to describe the relationship between life course overweight and the adipokines and inflammatory markers. For vWF, there was no evidence that the null model provided a poorer fit than the saturated model and so it was concluded that there was no effect of overweight at any age on vWF at age 60–64 years. Accumulation models including overweight at all three ages fitted the data as well as the saturated models for all other markers. The AIC for the model constraining the effect of overweight to be constant at all ages (‘strict’ accumulation model) had the lowest AIC for IL-6 and the model allowing the effect to vary across the three age points (‘relaxed’ accumulation) the lowest for leptin and CRP (Table 2). For the endothelial markers, E-selectin and t-PA, as well as for adiponectin, although the ‘relaxed’ accumulation model explained the data as well as the saturated model, the early old age sensitive period model had slightly smaller AICs. For consistency across types of markers, we thus investigated the relaxed accumulation model further for the adipokines and the inflammatory markers and the early old age model for the endothelial markers E-selectin and t-PA. We also investigated the early old age model for adiponectin and the strict accumulation model for adiponectin as the best fitting models according to the AIC.

Details of the selected life course models controlling for age, sex and potential confounders of smoking, childhood socioeconomic position and adult socioeconomic position are shown in Table 3. For adiponectin, leptin and CRP, after adjustment for overweight at the other two ages, the strengths of association with overweight increased with age. For IL-6, overweight at 60–64 years
years had the strongest association, followed by overweight at 15 years and then at 36 years. E-selectin and t-PA were, respectively, 16.2% (10.2, 22.5) and 34.3% (25.2, 44.0) higher for participants who were overweight compared with those not overweight at the age of 60–64 years. Adjustment for smoking status at age 60–64 years increased the strength of these associations slightly for adiponectin, CRP, E-selectin and IL-6, whereas adjustment for both childhood and adulthood socioeconomic measures reduced these associations slightly, but relationships remained strong after full adjustment.

All results were similar when alternative ages (20 rather than 15 years, 26 or 43 rather than 36 years, and 53 rather than 60–64 years) were used to test the fit of life course overweight models (data not shown). Exclusion of participants with CRP levels indicative of acute infection (≥10) eliminated associations of overweight at age 2 with CRP and adiponectin but did not substantially alter other associations or life course modelling conclusions (data not shown). Excluding those with a self-report of CVD or stroke at age 53 or 60–64 years only altered associations slightly, both higher and lower, with interpretation of results not changed (data not shown). Results from models using multiple imputations were largely consistent with results from the complete case analyses. Associations of adiponectin with overweight at 2 years and e-selectin with 15 years were attenuated in the multiple imputation analysis, while associations of adiponectin and e-selectin with overweight at 20 years were apparent in the multiple imputation and not the complete case analysis (Supplementary Table S9).

**DISCUSSION**

In this cohort of British men and women followed prospectively from birth in 1946 until age 60–64 years, greater accumulation of overweight across adolescence and adulthood was associated with higher adverse levels of several adiposopathic markers, particularly adipokines and inflammatory markers, which are closely implicated in the development of the atherosclerotic process. A slightly different pattern was seen for the endothelial makers of E-selectin and t-PA, where overweight at 60–64 years was particularly important.

The finding that overweight status was associated with levels of adiponectin, leptin, CRP and IL-6 is consistent with many previous studies showing that excess body fat in adulthood is associated cross-sectionally with adverse levels of these adipokines and inflammatory markers. However, the current analyses extend earlier reports by including a wider range of adiposopathic markers, including markers of endothelial dysfunction. We were able to show that, even though all of the outcomes measured for this study are a part of the same adiposopathic pathway, differences between overweight and non-overweight study members were much larger for leptin than the other markers. This could be explained by the fact that leptin is a very strong marker of total body fat status and a key regulator of energy intake and expenditure through appetite, metabolism and behaviour. Adiponectin is also directly released by adipose tissue, but is less directly related to body fat, potentially because of differences in how each adipokine is expressed in fat cells, structure and regulation. As the changes in inflammatory and endothelial marker concentrations could be a consequence of the
changes in adipokines, it is logical that strengths of association would be weaker. The absence of a consistent association between overweight status and vWF is consistent with earlier reports showing that vWF is less consistently associated with body fatness than other endothelial function markers.30,31

The current report is also important in showing that not only does being overweight at one period in time equate to more adverse levels of adipokines and inflammatory markers but also that continuing to stay overweight in adulthood will lead to increasingly adverse levels of these adiposopathic markers. A large number of randomised controlled trials have documented that weight loss in adulthood (generally 4–5%) can lead to lower levels of leptin,17,18 CRP and IL-6 (refs 14,17) and higher levels of adiponectin.14,17,18 Randomised controlled trials that did not find an effect of weight loss tended to be of short duration (<8 weeks) or small sample sizes. In observational longitudinal studies, the Cardiovascular Health Study found that weight loss in older adults over a 3-year period was associated with lower CRP, whereas weight gain was associated with higher CRP,15 and increases in waist circumference of Afro-Jamaican women over an average of 4.1 years was associated with lower adiponectin levels.16

Explanations for why the strength of associations between overweight status and adiposopathic markers increased with age are unknown. One possibility is that the estimates are actually the same across adulthood, but that associations for earlier adult ages appear weaker owing to BMI measurements being taken further away in time from when the adiposopathic markers were assessed. A more likely explanation is that study members who were overweight at one age were likely to be overweight at the next age (that is, tracking), with those overweight longer likely to have higher BMIs on average;32 and hence there would be larger differences in the adiposopathic markers between the overweight and non-overweight groups at later ages. Tracking of overweight over the life course is also why associations of overweight at earlier years with markers were reduced after adjustment for overweight at 60–64 years. Even with strong effects of overweight at older ages, estimates after adjustment for current overweight, and the results of the structured modelling approach, indicated that overweight at periods earlier than 60–64 years were important for adiposopathic marker levels at 60–64 years.

There was also evidence that differences in the adiposopathic markers at age 60–64 years for overweight compared with non-overweight widened over adulthood faster for some markers than others. This is the explanation for why the best fitting model chosen for each adiposopathic marker was generally some form of an accumulation model, but with heterogeneity in the type of accumulation. For example, the best fitting life course model chosen for IL-6 was the strict accumulation model because increases in associations were relatively small and consistent over time. For adiponectin and leptin, increases in associations by age increased stepwise from ages 15–36 to 60–64, resulting in a life course model chosen where the effect of overweight accumulates over time, but being overweight at older ages has more of an effect than being overweight earlier in adulthood.

For E-selectin and t-PA, effects of overweight appeared to be particularly strong for the cross-sectional measurement (60–64 years), but the possible influence of overweight at earlier periods should not be discounted. Similar to the inflammatory and endothelial markers, overweight during adolescence and adulthood was associated with the endothelial markers. That all associations were explained by overweight at 60–64 suggests that all relationships seen for overweight at earlier years could be due to tracking of body fatness. However, the finding that model fit for the sensitive period at 60–64 and the accumulation models were very similar suggests that overweight in adolescence and young

Figure 3. Percentage difference (95% CI) in inflammatory makers at age 60–64 years for overweight (BMI > 25 kg m\(^{-2}\)) vs normal weight, fitted separately for each age. Black lines indicate adjustment for age and sex only. Grey lines indicate further adjustment for overweight status at age 60–64 years. CI, confidence interval.
Results of $P$-values for partial F-tests, and AIC, comparing each represented life course models to a saturated model presented for each adiposopathic marker separately ($n = 1280$)

| Life course overweight and adiposopathic markers | Adipokine | Experimental markers | CRP | IL-6 |
|--------------------------------------------------|-----------|----------------------|-----|------|
| Adipokine | E-selectin | P-value | AIC | P-value | AIC | P-value | AIC | P-value | AIC |
| Saturated model | 0.00 | 2493.34 | 2454.81 | 2230.56 | 2035.95 | 0.00 | 3269.20 | 0.00 | 2624.45 |
| Sensitive period (years) | | | | | | | | | |
| Adolescence (15) | 0.00 | 2454.81 | 2230.56 | 2035.95 | 0.00 | 3269.20 | 0.00 | 2624.45 |
| Adulthood (36) | 0.00 | 2487.77 | 2230.56 | 2035.95 | 0.00 | 3269.20 | 0.00 | 2624.45 |
| Early old age (60–64) | 0.00 | 2487.77 | 2230.56 | 2035.95 | 0.00 | 3269.20 | 0.00 | 2624.45 |
| Accumulation | | | | | | | | | |
| Adolescence+adulthood | 0.00 | 2493.34 | 2230.56 | 2035.95 | 0.00 | 3269.20 | 0.00 | 2624.45 |
| Adulthood+early old age | 0.00 | 2493.34 | 2230.56 | 2035.95 | 0.00 | 3269.20 | 0.00 | 2624.45 |
| All three, strict | 0.00 | 2493.34 | 2230.56 | 2035.95 | 0.00 | 3269.20 | 0.00 | 2624.45 |

Abbreviations: AIC, Akaike Information Criteria; CRP, C-reactive protein; IL-6, interleukin-6; t-PA, tissue plasminogen activator; vWF, von Willebrand factor. A higher P-value for the life course model equals a better saturated model. A sensitive period model refers to testing whether being overweight at one age only (15, 36 or 60–64) is a better predictor of the adiposopathic marker at age 60–64 years. An accumulation model indicates that associations of overweight at each age can have different strengths. A strict accumulation model indicates strengths of association are equal for all the three ages. Bold values indicate $P < 0.05$.

Adipokines are inflammatory markers at late middle age.

In conclusion, we provide evidence that the longer an individual is overweight during adolescence and adulthood, the more adversely their level of adipokines and inflammatory markers at 60–64 years. Given that children alive today are likely to spend more of their lives as overweight or obese than study members in this study, with 33.9% of children in England currently being overweight or obese by the age of 10–11 years, compared with only 10.2% for NSHD at the same age, the differences seen in these adiposopathic markers between overweight and normal weight individuals could be even larger when current generations reach retirement age. The results suggest that the prevention of excess adiposity early in the life course could be important for the
and obesity in early adult life or earlier could have appreciable prevention of CVD in adult life. In addition, many of these adiposopathic risk factors are related to type 2 diabetes risk as well as to CVD. Therefore, preventing the development of overweight and obesity in early adult life or earlier could have appreciable benefit for the prevention of type 2 diabetes as well as CVD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table 3. Percentage increase (95% CI) of each adiposopathic marker for the selected life course model (n = 1280)

| Age and sex only | +Smoking status | +Childhood SEP | +Adulthood SEP | Full model |
|-----------------|----------------|---------------|---------------|-----------|
| **Adiponectin (years)** | | | | |
| 15 | 2.2 (−0.3, 16.4) | 0.7 (−11.6, 14.7) | 2.2 (−10.2, 16.4) | 2.3 (−10.3, 16.5) |
| 36 | −6.3 (−13.9, 2.0) | −4.7 (−12.7, 4.0) | −6.0 (−13.7, 2.3) | −6.6 (−14.3, 1.8) |
| 63 | −24.3 (−30.4, −17.7) | −26.1 (−32.2, −19.4) | −23.8 (−30.0, −17.2) | −24.2 (−30.3, −17.6) |
| **Leptin (years)** | | | | |
| 15 | 15.4 (1.5, 31.2) | 17.8 (3.3, 34.4) | 15.4 (1.5, 31.2) | 17.0 (2.9, 33.1) |
| 36 | 26.6 (16.4, 37.6) | 23.1 (12.6, 34.4) | 25.8 (15.7, 36.8) | 26.0 (15.8, 37.1) |
| 63 | 135.9 (117.2, 156.2) | 135.0 (115.4, 156.4) | 133.4 (114.8, 153.6) | 135.6 (117.0, 153.9) |
| **CRP (years)** | | | | |
| 15 | 10.1 (−7.5, 31.0) | 10.3 (−7.7, 31.8) | 10.2 (−7.4, 31.1) | 12.6 (−5.4, 33.9) |
| 36 | 14.4 (2.1, 28.1) | 13.9 (10.8, 24.4) | 13.1 (9.0, 26.6) | 13.9 (1.7, 27.7) |
| 63 | 37.0 (22.5, 53.1) | 39.1 (23.6, 56.5) | 34.3 (20.1, 50.3) | 35.5 (21.2, 51.4) |
| **Interleukin-6 (years)** | | | | |
| 15 | 16.4 (1.5, 33.6) | 19.1 (3.7, 36.8) | 16.5 (1.6, 33.7) | 18.3 (3.1, 35.7) |
| 36 | 11.1 (1.6, 21.5) | 8.9 (−0.8, 19.6) | 10.1 (0.7, 20.5) | 10.6 (1.1, 21.1) |
| 63 | 20.1 (10.0, 31.2) | 20.7 (10.1, 32.3) | 18.5 (8.4, 29.5) | 19.5 (9.4, 30.5) |
| **Early old age sensitive period model (50–64 years only)** | | | | |
| Adiponectin | −30.1 (−37.8, −22.3) | −32.0 (−39.9, −24.1) | −29.5 (−37.3, −21.7) | −29.8 (−37.6, −22.0) |
| E-selectin | 16.2 (10.2, 22.5) | 17.5 (11.1, 24.2) | 15.4 (9.4, 21.8) | 16.1 (10.0, 22.4) |
| Tissue plasminogen activator | 34.3 (25.2, 44.0) | 31.3 (21.9, 41.3) | 33.9 (24.7, 43.7) | 34.2 (25.1, 44.0) |

Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; SEP, socioeconomic position. aOverweight compared with non-overweight at 15, 36 or 60–64 years, adjusted for overweight status for the other 2 years. bThe ‘strict’ accumulation model was chosen as the best fitting life course model for IL-6, but P-values were similar to the ‘relaxed’ accumulation model, so we have shown the latter model here to compare coefficients for overweight at each age with the other inflammatory marker. cOverweight compared with non-overweight at age 60–64 years.
Supplementary Information accompanies this paper on International Journal of Obesity website (http://www.nature.com/ijo)