Association between change in body composition and change in inflammatory markers: an 11-year follow-up in the Whitehall II Study.

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Abstract

Context

Obesity is associated with low-grade inflammation, but the long-term effects of weight change on inflammation are unknown.

Objective

To examine the association of change in weight, body mass index (BMI) and waist circumference with change in C-reactive protein (CRP) and interleukin-6 (IL-6), and to assess whether this association is modified by baseline obesity status.

Design and Setting

A prospective cohort study among civil servants (the Whitehall II study, UK). We used data from two clinical screenings carried out in 1991–1993 and 2002–2004 (mean follow-up 11.3 years).

Participants

2496 men and 1026 women (mean age 49.4 [SD=6.0] years at baseline) with measurements on inflammatory markers and anthropometry at both baseline and follow-up.

Main Outcome Measures

Change in serum CRP and IL-6 during follow-up.

Results

The mean increases in CRP and IL-6 were 0.08 (95% CI: 0.07–0.09) mg/L and 0.04 (95% CI: 0.03–0.05) pg/L per 1-kg increase in body weight during follow-up. Study members with a BMI<25 kg/m^2 at baseline had an average increase in CRP of 0.06 (95% CI: 0.05–0.08) mg/L per 1-kg increase in body weight, while the increase in those who were overweight (25≤BMI<30 kg/m^2) and obese (BMI≥ 30 kg/m^2) was greater: 0.08 (95% CI 0.06–0.09) mg/L and 0.11 (95% CI: 0.07–0.14) mg/L, respectively (P-value for interaction=0.002). Similar patterns were observed for changes in BMI and waist circumference.

Conclusions

Those who were overweight or obese at baseline had a greater absolute increase in CRP per unit increase in weight, BMI and waist circumference, than people who were normal weight.

Author Keywords Weight ; Body Mass Index ; waist circumference ; inflammation ; CRP ; IL-6

MESH Keywords Adult ; Biological Markers ; blood ; Body Composition ; physiology ; Body Height ; Body Mass Index ; Body Weight ; C-Reactive Protein ; metabolism ; Cohort Studies ; Female ; Follow-Up Studies ; Humans ; Inflammation ; blood ; epidemiology ; metabolism ; Interleukin-5 ; blood ; Male ; Middle Aged ; Obesity ; blood ; complications ; metabolism ; Waist Circumference ; Weight Gain ; physiology

INTRODUCTION

Low-grade systemic inflammation is associated with atherosclerosis and other chronic conditions such as diabetes (1 ,2). C-reactive protein (CRP, a plasma protein synthesized by the liver) and interleukin-6 (IL-6, a cytokine that governs inflammatory cascades and modulates CRP) are key biochemical markers of inflammation (3 ,4). It is well established that overweight and obese persons have, on average, higher concentrations of CRP and other inflammatory markers than their leaner counterparts. (5 ,6). It has also been shown that intentional weight loss leads to reduced inflammatory marker levels in the short term (7 ,8). However, the long-term associations of change in weight or central obesity with changes in inflammatory markers in larger populations are poorly understood (9 ,10). Accordingly, we assessed how changes in weight, BMI, and waist circumference over a period of 11 years were associated with changes in CRP and IL-6 in a large cohort of middle-aged British adults (11). We also examined whether weight-related changes in inflammatory markers differed between normal weight, overweight and obese individuals.

MATERIALS AND METHODS

Study population

Whitehall II, a prospective cohort study, was established in 1985. Participants were all office staff, aged 35–55 years at enrolment and working in 20 London-based Civil Service departments. In total, 10,308 people (6895 men and 3413 women), 73% of those invited, were included at baseline (1985–1988) (11). Initial cohort members were subsequently invited to participate in seven data collection phases.

In the present analysis, we utilised data from phases three (1991–1993) and seven (2002–2004) – the only occasions when CRP and IL-6 were measured. After excluding participants who reported having had a cold or flu in the 14 days preceding blood collection, or had a CRP over 10 mg/L at either phase three or seven, a total of 3522 participants (2496 men and 1026 women) had values on inflammatory markers and anthropometric measures from both phases three and seven; this being our analytical sample (Supplemental table S1). The mean follow-up time between phase three and phase seven was 11.3 years (range 9.5–12.9 years).

The Whitehall II study has approval from the University College London Medical School Committee on the Ethics of Human Research. Informed consent was gained from all participants.

Anthropometry

Data on weight, height and waist circumference were collected by trained study nurses at clinical screening sessions both at phase three and seven. Weight was measured to the nearest 0.1 kg. Height was measured with participants standing erect with their head in the Frankfort plane, and was recorded to the nearest 0.1 cm. BMI was calculated as weight (kg)/height $(m)^2$. Waist circumference was measured halfway between the costal margin and the iliac crest; measurements were recorded to the nearest 0.1 cm.

Inflammatory markers

Fasting serum was collected between 0800 and 1300 hours and was stored at −70°C. Samples from phases three and seven were analysed at the same time. CRP was measured using a high-sensitivity immunonephelometric assay in a BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK). IL-6 was measured using a high-sensitivity enzyme-linked immunosorbent assay (R&D Systems, Oxford, UK). Values lower than the detection limit (0.154 mg/L for CRP and 0.08 pg/mL for IL-6) were assigned a value equal to half the detection limit.

Covariates

Covariates included in the present study, measured at baseline were: age, ethnicity (White, South Asian, Black, other), socioeconomic position based on civil service employment grade (low, intermediate, high), smoking (never smoker, ex-smoker, current smoker), and leisure-time physical activity (none or mild physical activity vs. moderate activity at least 3 times or vigorous activity at least 1–2 times per week). Coronary heart disease (CHD) was defined by using the Multinational Monitoring of trends and determinants in cardiovascular disease (MONICA) criteria (12). Diabetes was defined by a fasting glucose of 7·0 mmol/L or more; a 2-h postload glucose of 11·1 mmol/L or more; self-report of doctor diagnosis; or use of diabetes medication (13).

Statistical analysis

The distributions of CRP and IL-6 at baseline and follow-up were skewed, so the geometric means and standard deviations of logged values are presented for these variables. The distributions for the 6(13) changes in CRP and IL-6 between phases three and se ven were not skewed, so the arithmetic means and standard deviations are presented for these variables.

Multivariable linear regression models were used to evaluate the relationships of change in weight, BMI and waist circumference (exposure variables) with changes in CRP and IL-6 (outcome variables). Throughout these analyses we simultaneously took into account the effect of a range of potential confounding factors. To examine whether the association was dependent on baseline obesity status, we stratified analyses by the following baseline categories of BMI: underweight/normal weight (BMI<25.0); overweight (25.0≤BMI<30.0);

and obese (BMI≥30.0) (14). Statistical interaction was evaluated by including product terms between baseline BMI category and the exposure variable of interest in the respective models (i.e., weight change, BMI change or change in waist during the follow-up). These analyses were performed separately for the two outcome measures.

All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA, 2002–2003).

RESULTS

In the analytical sample, mean age at baseline (phase three) was 49.4 (SD=6.0) years; men constituted 71% of the sample; and most study participants were white (Table 1). Mean weight increased in this sample by 3.0 (SD=5.8) kg over 11 years of follow-up. The increase in BMI and waist circumference was 1.4 (SD=2.0) kg/m^2 and 7.7 (SD=7.4) cm for all participants. On average, CRP increased by 0.53 (SD=1.81) mg/L and IL-6 by 0.45 (SD=1.79) pg/mL.

The crude changes in mean CRP and IL-6 during the follow-up by quartiles of change in weight, BMI, and waist circumference, are shown in Supplemental Figure S1. These data suggest a linear association between increase in inflammatory markers and increase in weight, BMI and waist circumference. Linear regression showed a one kg increase in body weight over the 11 years of follow-up to be associated with a mean increase in CRP of 0.08 (95% confidence interval (CI) 0.07–0.09) mg/L, while the corresponding increase in IL-6 was 0.04 (95% CI 0.03–0.05) pg/mL (Table 2). The relationship between change in weight and BMI in relation to change in CRP was stronger among women than men ($P_{\text{'Sex x change in weight' interaction}}$ <0.0001 and $P_{\text{'Sex x change in BMI' interaction}}$ =0.0004,), while no sex differences were noted in the associations between change in weight, BMI or waist circumference, and IL-6.

In analyses stratified by baseline BMI categories, the relationship between change in the anthropometric measures and change in CRP was stronger in those overweight and obese at baseline, as compared with those who were lean or normal weight at baseline (Table 2). This observation was unchanged irrespective of whether we used change in weight ($P_{\text{Baseline BMI category x change in weight' interaction}}$ =0.002), BMI ($P_{\text{'Baseline BMI category x change in BMI' interaction}}$ =0.003) or waist circumference ($P_{\text{'Baseline BMI category x change in waist' interaction}}$ <0.0001) as the exposure variable in the models. For example, the average change in CRP was 0.31 (95% CI 0.22–0.40) mg/L per unit change in BMI in the obese group, while the corresponding figure in the overweight and lean/normal weight groups were 0.22 (95% CI 0.17–0.27) mg/L and 0.18 (95 % CI 0.14–0.22) mg/L, respectively. A similar pattern, albeit weaker, was observed in relation to change in IL-6, but only the interaction between change in waist circumference and baseline BMI category was statistically significant (P=0.002).

To test the robustness of our findings, we repeated the main multivariable linear regression analyses of weight change and change in inflammatory markers after excluding participants who had any CHD up to and including phase three (n=266), type 2 diabetes at phase three (n=78), as well as those who reported taking lipid-lowering drugs any time during follow-up (n=420)(note that lipid lowering medication may affect levels of inflammation). In these analyses our conclusions were essentially unchanged (results not shown but available upon request).

DISCUSSION

We found that CRP and IL-6 levels increased over an 11-year follow-up period in a middle-aged population. The size of this increase in inflammatory markers was associated with the change in weight, BMI or waist circumference. These associations were more pronounced among those who were overweight or obese at baseline relative to normal weight persons.

The strengths of this study are use of multiple indicators of both adiposity and inflammation, and a large sample size. With little difference between the characteristics of participants at baseline and those included in this analytical sample, there was no strong evidence of selection bias (supplementary table S1). However, our study uses observational data, which can never provide complete inferences about causality.

In a UK community-based cohort study of 1222 participants followed over 9 years, an average increase in CRP of 0.09 mg/L per kg increase in weight was observed, which is consistent with our findings (9). Our findings also accord with a French study of 1099 middle-aged participants which found significant correlations between change in BMI, waist-hip ratio and waist girth, and change in CRP, haptoglobin, orosomucoid, and between change in waist-hip ratio and waist girth and change in white blood cells, over a period of 5 years (10).

To our knowledge, this is the first study to report that those who are obese may have a greater absolute increase in CRP per unit increase in subsequent weight, BMI and waist circumference, than those who are normal weight. This observed effect is plausible. Obese persons are known to have enlarged adipocytes (8 ,15), and adipose tissue in obese persons shows higher expression of several pro-inflammatory proteins as compared with adipose tissue in leaner persons (15 ,16). It has been shown that both high BMI and increased adipocyte size predict a proportionally higher macrophage infiltration and accumulation in adipose tissue, increasing cytokine production in obese adipose tissue (16 ,17). Mouse models have demonstrated that diet-induced obesity leads to a shift in the adipose

tissue macrophage type, from the anti-inflammatory alternatively-activated type to the pro inflammatory classically-activated type (18). Furthermore, a higher incidence of pro-inflammatory co morbidities, such as osteoarthritis, has been observed among obese persons (19). Additional research is needed to examine whether these and other mechanisms may be responsible for the interaction effect observed in our study.

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Footnotes:

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TABLE 1

Baseline characteristics and changes between baseline at follow-up (Δ) in obesity measures and inflammatory markers of the study sample with full measurements on inflammatory markers and anthropometry at both baseline (phase three, 1991–1993) and follow-up (phase seven, 2002–2004), the Whitehall II study.

	All n=3522	**Men n=2496**	**Women n=1026**
Age years [mean (S.D.)]	49.4 (6.0)	49.3 (6.0)	49.7 (6.0)
Ethnicity [n (%)]			
White	3224 (92)	2330 (93)	894 (87)
South Asian	168 (5)	110 (4)	58 (6)
Black	96 (3)	36 (1)	60 (6)
Other	31 (1)	18 (1)	13 (1)
Civil Service Grade [n (%)]			
High	1441 (41)	1242 (50)	199 (20)
Intermediate	1606 (46)	1124 (46)	482 (47)
Low	438 (13)	103 (4)	335 (33)
Smoking [n (%)]			
Never Never-smoker	1825 (53)	1235 (51)	590 (59)
Ex Ex-smoker	1226 (36)	951 (39)	275 (275)
Current smoker	383 (11)	253 (10)	130 (130)
Exercise level [n (%)]			
High	1107 (32)	909 (37)	198 (19)
Low	2382 (68)	1564 (63)	818 (81)
CHD up to and including phase three [n (%)]			
No	3256 (92)	2331 (93)	952 (90)
Yes	266 (8)	165 (7)	101 (10)
Diabetes type 2 at phase three [n (%)]			
No	3444 (98)	2440 (98)	1004 (98)
Yes	78 (2)	56 (2)	22 (2)
Weight kg [mean (S.D.)]	74.4 (12.2)	77.6 (10.7)	66.7 (12.4)
BMI kg/m ^{2} [mean (S.D.)]	25.0 (3.6)	24.9 (3.0)	25.3 (4.6)
Waist circumference cm [mean (S.D.)]	85.1 (11.3)	88.5 (9.1)	76.8 (11.9)
CRP mg/L [G-mean ($S.D._{log}$)][1]	0.75 (1.09)	0.72 (1.08)	0.84 (1.10)
IL-6 pg/mL [G-mean ($S.D._{log}$)][1]	1.42 (0.56)	1.36 (0.53)	1.58 (0.60)
ΔWeight kg [mean (S.D.)][2]	3.0 (5.8)	3.0 (5.5)	2.9 (6.3)
ΔBMI kg/m2 [mean (S.D.)][2]	1.4 (2.0)	1.4 (1.8)	1.5 (2.4)
ΔWaist cm [mean (S.D.)][2]	7.7 (7.4)	6.5 (6.1)	10.5 (9.4)
ΔCRP mg/L [mean (S.D.)][2]	0.53 (1.81)	0.45 (1.75)	0.73 (1.95)
ΔIL-6 pg/mL [mean (S.D.)][2]	0.45 (1.79)	0.57 (1.71)	0.15 (1.9)

[1] Geometric mean and standard deviation of logged values
[2] Δ=change between baseline and follow-up

TABLE 2

Change (Δ) in CRP and IL-6 values between baseline and follow-up per unit change in weight (kg), BMI (kg/m^2), and waist circumference.[1]

		ΔCRP mg/L			ΔIL-6 pg/mL		
		n	**beta (95% CI)[2]**	**p-value for interaction**	**n**	**beta (95% CI)[2]**	**p-value for interaction**
ΔWeight kg		3401	0.08 (0.07–0.09)		3132	0.04 (0.03–0.05)	
ΔBMI kg/m^2		3392	0.23 (0.20–0.26)		3126	0.12 (0.09–0.15)	
ΔWaist cm		3363	0.05 (0.04–0.06)		3095	0.03 (0.02–0.04)	
By sex							
ΔWeight kg	Men	2417	0.06 (0.05–0.07)	<0.0001	2236	0.04 (0.03–0.06)	0.64
ΔWeight kg	Women	984	0.11 (0.09–0.13)		896	0.04 (0.02–0.06)	
ΔBMI kg/m^2	Men	2411	0.19 (0.15–0.22)	0.0004	2232	0.14 (0.09–0.18)	0.25
ΔBMI kg/m^2	Women	981	0.29 (0.24–0.34)		894	0.11 (0.05–0.16)	
ΔWaist cm	Men	2385	0.05 (0.04–0.06)	0.39	2205	0.03 (0.02–0.05)	0.17
ΔWaist cm	Women	978	0.06 (0.04–0.07)		890	0.02 (0.01–0.03)	
By BMI at baseline							
ΔWeight kg	BMI<25	1888	0.06 (0.05–0.08)	0.002	1753	0.03 (0.01–0.05)	0.22
ΔWeight kg	25≤BMI<30	1243	0.08 (0.06–0.09)		1143	0.05 (0.03–0.06)	
ΔWeight kg	BMI≥30	263	0.11 (0.07–0.14)		231	0.05 (0.02–0.09)	
ΔBMI kg/m^2	BMI<25	1887	0.18 (0.14–0.22)	0.003	1753	0.09 (0.05–0.14)	0.43
ΔBMI kg/m^2	25≤BMI<30	1243	0.22 (0.17–0.27)		1143	0.13 (0.07–0.18)	
ΔBMI kg/m^2	BMI≥30	262	0.31 (0.22–0.40)		230	0.15 (0.05–0.25)	
ΔWaist cm	BMI<25	1863	0.04 (0.03–0.05)	<.0001	1729	0.02 (0.01–0.03)	0.002
ΔWaist cm	25≤BMI<30	1231	0.05 (0.03–0.06)		1132	0.02 (0.01–0.04)	
ΔWaist cm	BMI≥30	262	0.11 (0.07–0.14)		230	0.08 (0.05–0.12)	

Δ=change between baseline and follow-up
[1] Participants with CRP values greater than 10 mg/L at baseline or follow-up, or having cold/flu during the last 14 days before blood sampling at baseline or follow-up were excluded.
[2] Adjusted for sex, ethnicity, baseline age, socio-economic position (civil service grade), smoking, physical activity, and baseline weight/BMI/waist circumference.