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Inflammation, Adiposity, and Mortality in the Oldest Old

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Abstract

Background: Increased proinflammatory status is associated with both increased adiposity and higher mortality risk. Thus, it is paradoxical that mild obesity does not predict increased mortality in older adults. We investigated the association of inflammatory markers with body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR) in nonagenarians, and the combined effects of BMI, WC, WHR, and inflammatory status on mortality.
Methods: This study was based on a prospective population-based study, Vitality 90+, carried out in Tampere, Finland. Altogether, 157 women and 53 men aged 90 years were subjected to anthropometric measurements, blood samples, and a 4-year mortality follow-up. Inflammatory status was based on sex-specific median levels of interleukin-1 receptor antagonist (IL-1RA), interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α).
Results: In the unadjusted linear regression analyses, IL-1RA, CRP, and TNF-α were positively associated with BMI and WC in women, whereas in men IL-1RA was positively associated with BMI and IL-6 positively with WC. In the models adjusted for diseases, functional status, and smoking, IL-1RA and CRP were positively associated with BMI and WC in women. Low WC and WHR combined with low inflammation protected from mortality in women and high BMI and WC regardless of inflammation protected from mortality in men in the adjusted Cox regression analysis.
Conclusions: In the oldest old, the effect of adiposity in combination with inflammatory status on mortality differs between men and women. More research is needed to disentangle the role of adiposity among the oldest old.

Introduction

It has become evident that white adipose tissue represents a dynamic endocrine organ that secretes several hormones and other proteins, including many inflammatory markers.[1] Circulating levels of inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1RA), and tumor necrosis factor-α (TNF-α) have been reported in younger to older adults to be positively associated with increased adiposity, measured as body mass index (BMI), waist circumference (WC), or waist-to-hip ratio (WHR).[2–4] A wealth of data supports the view that the low-grade proinflammatory state has an essential role as the origin and maintainer of many chronic diseases, such as cardiovascular disease, cancer, or Alzheimer disease.[5–7] In addition, increased inflammatory status is associated with the process of aging[8] and with increased mortality risk.[9]

Inflammatory status is strongly associated with adiposity and with mortality, thus it is paradoxical that overweight and mild obesity do not predict increased mortality in older adults.[10] The relationships between adiposity, inflammation, and mortality have been previously discussed concerning chronic kidney disease.[11] Recently, Lakoski et al.[12] directly addressed the interactions between adiposity, inflammation, and mortality in middle-aged to older adults, showing that elevated CRP was a more powerful risk factor for mortality in underweight and normal weight compared to overweight or obese persons, and also that racial differences existed. However, the area is still scantily studied, and data especially on very old people are lacking. In general, there is also a paucity of data concerning the associations between inflammatory markers and adiposity in the oldest old.

Previously, we have examined the associations of inflammatory markers[13] and adiposity (BMI, WC, and WHR)[14]

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with mortality in nonagenarians. Regarding inflammation, IL-RA was a particularly powerful prognostic marker for mortality.[13] Regarding adiposity, low BMI increased mortality risk, especially in men, but the combination of high BMI and low WC seemed to be protective for both women and men.[14]

The purpose of this study was, first, to investigate cross-sectional associations between BMI, WC, and WHR and inflammatory markers (IL-1RA, IL-6, CRP, and TNF-α), and, second, to examine the combined effects of inflammatory markers and adiposity on mortality in 90-year-old people.

Methods

Participants and study design

The data are from the Vitality 90+ Study, which is a prospective, multidisciplinarym population-based study of people aged 90 or older living in the area of Tampere, Finland. The study population in this study consisted of all people born in 1909–1910, who, according to the local population register, were living in the city of Tampere ($n = 535$) as of January, 2000. Both community-dwelling and institutionalized persons were invited to participate in home interviews, anthropometric measurements, and blood sampling. According to the National Population Register Center, 66 persons died before the beginning of data collection. Another 42 persons died during the study but before being examined, leaving 427 persons eligible for the study. An additional 86 persons refused to participate, mostly due to poor physical or mental condition, and 7 persons could not be reached. Another 45 persons participated, but refused the blood tests, and 79 persons were lacking at least one of the anthropometric measures or a result in at least one of the inflammatory markers. The final study population of 210 persons (49% of the eligible population) consisted of persons who had results in all of the anthropometric and inflammatory measures (157 women and 53 men).

Interviews, anthropometric measurements, and blood sampling were carried out in the year 2000 at homes for community-dwelling participants and in institutions for institutionalized participants. Medical diagnoses were collected from health center records. The study protocol was approved by the Ethics Committee of the Pirkanmaa Hospital District and the Ethics Committee of Tampere Health Center. All participants or their legal representatives gave their written informed consent.

Anthropometric measurements

The anthropometric measurements included height, weight, WC, and hip circumference. Height was measured to the nearest 1 cm and weight to the nearest 1 kg. BMI was calculated as weight in kilograms divided by height in meters squared. Due to the small number of underweight (BMI < 18.50 kg/m^2; in women $n = 2$ and in men $n = 0$) and obese (BMI ≥ 30.00 kg/m^2; in women $n = 12$ and in men $n = 2$) subjects, BMI was classified as (1) < 25.00 kg/m^2 (low BMI) and (2) > 25.00 kg/m^2 (high BMI). WC was measured midway between the level of the iliac crest and the lowest rib and classified according to the sex-specific median (cutoff point for men 93 cm and for women 85 cm). Hip circumference was measured from the widest part of pelvis.[15] WHR was computed as the ratio of WC-to-hip circumference and classified according to the sex-specific median (cutoff point for men 0.91 and for women 0.85).

Biochemical measurements

Blood samples were collected in the morning after an overnight fast using EDTA tubes in ice. Plasma was separated after centrifugation (15 min at 700 × *g*), divided into aliquots, and stored at −80°C until analyzed. Concentrations of IL-6 and IL-1RA were analyzed using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Pelikine Compact human IL-6 ELISA kit, CLB, Amsterdam, The Netherlands for IL-6; Quantikine, R&D Systems, Minneapolis, MN for IL-1RA; The optical density of the wells was analyzed with a Multiscan Biochromatic 348 (Labsystems, Helsinki, Finland) spectrophotometer. Concentration of TNF-α was analyzed with a Luminex-based multiplex analysis system (Bio-Plex 200 System, BioRad Laboratories, Inc.) using a commercially available kit, (Human Serum Adipokine (Panel B) kit, catalog HADK-2-61K-B, LINKOplex). High-sensitivity CRP was analyzed using a Cobas Integra 700 automatic analyzer with reagents and calibrators as recommended by the manufacturer (Hoffman-La Roche Ltd., Basel, Switzerland; COBAS Integra C-reactive Protein, Latex). For CRP, some of the results were below the detection level of 0.10 mg/L. All values below the detection level were coded as 0.05 mg/L. The given inflammatory markers were selected on the basis of their availability, wide use in the literature, and reported association with levels of adiposity.

A separate variable to describe inflammatory burden was defined on the basis of how many markers out of IL-1RA, IL-6, CRP, and TNF-α had a higher level than the sex-specific median. Inflammatory status was categorized as: (1) 0–1 inflammatory markers above the sex-specific median (low inflammation) and (2) 2–4 inflammatory markers above the sex-specific median (high inflammation).

Mortality

Mortality follow-up was based on dates of death drawn from the Population Register Center. Follow-up time was calculated from February 21, 2000, to the date of death or to February 21, 2004, for survivors. There were no losses to mortality follow-up.

Other variables

Medical diagnoses were available for 187 participants. The diagnoses were collected from records maintained by public health care physicians including diagnoses made in hospitals, and coded according to the *International Classification of Diseases, 10th Revision* (ICD-10). History in cardiovascular disease, infectious disease, cancer (all cancers except for basal carcinoma), respiratory disease, and diabetes were chosen to describe the disease status of the participants. Functional status, assessed by Barthel index, was categorized into two groups: (1) 0–90 points (poor to moderate) or (2) 95–100 points (good). Smoking status was categorized as: (1) current or former or (2) never smoker.

Statistical analyses

Associations between BMI, WC, and WHR and inflammatory markers (IL-1RA, IL-6, CRP, and TNF-α) were analyzed by linear regression analysis. An unadjusted and an adjusted model were performed to analyze the association of

Table 1. Baseline Characteristics of the 90-Year-Old Study Population

Characteristics	*Women* n = *157*	*Men* n = *53*
Height, cm, mean (SD)	157.4 (6.1)	170.9 (7.2)
Weight, kg, mean (SD)	60.8 (10.1)	71.1 (9.9)
Body mass index (BMI), kg/m^2, mean (SD)	24.5 (3.5)	24.4 (3.3)
BMI categories, n (%)		
< 25.00 kg/m^2	95 (60.5)	34 (64.2)
≥ 25.00 kg/m^2	62 (39.5)	19 (35.8)
Waist circumference, cm, mean (SD)	85.8 (10.2)	94.4 (10.4)
Hip circumference, cm, mean (SD)	99.7 (8.6)	101.8 (7.7)
Waist-to-hip ratio, mean (SD)	0.86 (0.07)	0.93 (0.06)
IL-1RA, pg/mL, median (IQR)	364 (276–482)	360 (261–458)
IL-6, pg/mL, median (IQR)	2.40 (1.53–3.98)	2.90 (1.89–6.67)
CRP, mg/L, median (IQR)	1.20 (0.40–4.05)	1.90 (0.75–4.15)
TNF-α, pg/mL, median (IQR)	4.14 (2.99–5.46)	4.13 (2.99–5.28)
Inflammatory markers above the median[a], *n* (%)		
0 markers	18 (11.5)	5 (9.4)
1 marker	45 (28.7)	14 (26.4)
2 markers	29 (18.5)	17 (32.1)
3 markers	45 (28.7)	8 (15.1)
4 markers	20 (12.7)	9 (17.0)
Barthel index, *n* (%)		
0–90	54 (34.4)	18 (34.0)
95–100	103 (65.6)	35 (66.0)
Smoking status, *n* (%)		
Current or former smoker	6 (3.8)	19 (35.8)
Never smoker	151 (96.2)	34 (64.2)
History of diseases, *n* (%)		
Cardiovascular disease	108 (68.8)	35 (66.0)
Diabetes	11 (7.0)	4 (7.5)
Cancer	12 (7.6)	8 (15.1)
Respiratory disease	28 (17.8)	17 (32.1)
Infectious disease	58 (36.9)	27 (50.9)
Data missing	17 (10.8)	6 (11.3)
Living residence, *n* (%)		
Home	141 (89.8)	52 (98.1)
Institution	16 (10.2)	1 (1.9)

[a]Sex-specific median of plasma levels of CRP, IL-6, IL-1RA, and TNF-α.

SD, Standard deviation; BMI, body mass index; IL-1RA, interleukin-1 receptor antagonist; IQR, interquartile range; IL-6, interleukin-6; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α.

each anthropometric measure with each inflammatory marker. Adjustments were made for history of diseases (cardiovascular disease, cancer, diabetes, respiratory disease, and infectious disease), functional status, and smoking. Because of missing data in history of diseases, both the unadjusted and adjusted analyses were performed only for those participants who did not have any missing data.

Cox proportional hazards models were used to analyze the combined effects of BMI, WC, and WHR and inflammatory status with all-cause mortality over 4 years. BMI, WC, and WHR were each combined with inflammatory status, and in each of the 4-class variables, the lower value in anthropometric measure and low inflammation was the reference group. Adjustments were made for history of diseases (cardiovascular disease, cancer, diabetes, respiratory disease, and infectious disease), functional status, and smoking. Missing data in diseases was categorized as its own group. In addition, the adjusted 4-year mortality analyses were conducted only for those participants who survived the first 2 years of the follow-up ($n = 129$ in women and $n = 32$ in men). This was done to examine the role of reverse causality, that is, people may have low body weight because of fatal illness. Also the interactions in the mortality analyses between BMI, WC, and WHR and inflammatory status were analyzed for all. Statistical power was analyzed for the univariate Cox proportional hazards models.

The levels of inflammatory variables were not normally distributed. For normalizing the values, all inflammatory variables were $\log_{10}$ transformed. All of the analyses were performed separately for men and women. Analyses were carried out with SPSS for Windows (SPSS Inc., Chicago, IL) version 18.0. A significance level of $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the subjects are shown in Table 1. In the unadjusted analyses, BMI was positively associated with IL-1RA, CRP, and TNF-α in women (for each $p < 0.05$), and with IL-1RA ($p = 0.031$) in men (Table 2). After adjustment, BMI remained positively associated with IL-1RA and

Table 2. Linear Regression Analysis of the Associations of Body Mass Index, Waist Circumference, and Waist-to Hip Ratio with Inflammatory Markers[a] in 90-Year-Old Women and Men

	BMI		*WC*		*WHR*	
	Unadjusted	*Adjusted*	*Unadjusted*	*Adjusted*	*Unadjusted*	*Adjusted*
	β (p *value*)		*β* (p *value*)		*β* (p *value*)	
Women ($n=140$)						
IL-1RA	**0.401 (<0.001)**	**0.404 (<0.001)**	**0.349 (<0.001)**	**0.353 (<0.001)**	0.121 (0.155)	0.095 (0.270)
IL-6	0.035 (0.682)	0.008 (0.931)	0.029 (0.738)	−0.010 (0.910)	0.001 (0.989)	−0.047 (0.587)
CRP	**0.209 (0.013)**	**0.238 (0.008)**	**0.176 (0.038)**	**0.202 (0.022)**	−0.040 (0.638)	−0.047 (0.597)
TNF-α	**0.194 (0.021)**	0.165 (0.070)	**0.178 (0.035)**	0.131 (0.143)	0.030 (0.726)	−0.022 (0.801)
Men ($n=47$)						
IL-1RA	**0.314 (0.031)**	0.228 (0.143)	0.241 (0.103)	0.199 (0.192)	0.107 (0.475)	0.165 (0.301)
IL-6	0.210 (0.156)	0.149 (0.346)	**0.320 (0.028)**	0.264 (0.082)	0.173 (0.246)	0.194 (0.225)
CRP	−0.233 (0.115)	−0.299 (0.062)	−0.060 (0.687)	−0.225 (0.154)	0.103 (0.489)	−0.012 (0.942)
TNF-α	0.134 (0.370)	0.129 (0.451)	0.173 (0.246)	0.145 (0.385)	0.105 (0.483)	0.134 (0.440)

The results are shown by standardized betas with p values. Models were performed separately for each BMI, WC, and WHR.

Unadjusted analysis: Models were performed separately for each inflammatory marker (IL-1RA, IL-6, CRP, and TNF-α).

Adjusted analysis: Adjusted for history of diseases (cardiovascular disease, cancer, diabetes, respiratory disease, and infectious disease), functional status, and smoking. Models were performed separately for each inflammatory marker (IL-1RA, IL-6, CRP, and TNF-α).

[a]Values are transfered to $\log_{10}$

BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; IL-1RA, interleukin-1 receptor antagonist; IL-6, interleukin-6; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α.

CRP in women ($p<0.05$). In men, the negative association between BMI and CRP was borderline significant ($p=0.062$) after adjustment. In the unadjusted analyses, WC was positively associated with IL-1RA, CRP, and TNF-α in women ($p<0.05$) and with IL-6 ($p=0.028$) in men. After adjustment, WC remained positively associated with IL-1RA and CRP in women ($p<0.05$), whereas no significant associations were found in men. WHR was not associated with any inflammatory marker in any analyses.

In women, no significant results were found regarding BMI in the adjusted mortality analyses (Table 3). In men, the adjusted mortality risk was significantly lower with high BMI and low inflammation (hazard ratio [HR] 0.13, 95% confidence interval [CI] 0.03–0.59) and with high BMI and high inflammation (HR 0.25, 95% CI 0.09–0.76) compared to low BMI and low inflammation. Regarding WC and WHR, in women the adjusted mortality risk was significantly higher in all the other groups when low WC or WHR and low inflammation was the reference group. For WC, the highest mortality risk was with high WC and low inflammation (HR 7.23, 95% CI 2.70–19.39), and for WHR the highest mortality risk was with low WHR and high inflammation (HR 4.69, 95% CI 1.64–13.46), respectively. On the contrary, in men mortality risk was significantly lower with high WC and low inflammation (HR 0.13, 95% CI 0.03–0.59) and with high WC and high inflammation (HR 0.25, 95% CI 0.09–0.76) compared to low WC and inflammation in the adjusted analyses.

When people who died during the first 2 years of the follow-up were excluded from the adjusted analyses, in women only the results regarding WC and inflammatory status remained statistically significant, similarly to the main analyses. In men, the results for BMI and WC did not show any marked change, but due to the very low number of observations the results cannot be considered reliable (data not shown.)

In the mortality analyses, in women the interactions between WC and inflammatory status ($p<0.001$) and WHR and inflammatory status ($p=0.002$), respectively, were statistically significant (data not shown). There was also a tendency for a significant interaction between BMI and inflammatory status in women ($p=0.07$). In men, no interactions were found.

The statistical power in women in the mortality analyses concerning WC and WHR was at a good level (range 95.9%–99.7%), but concerning BMI the values (range 10.7%–75.7 %) did not reach a level considered sufficient. In men, the statistical power in all the mortality analyses was low (range 5.4%–27.0 %), which was also expected on the basis of the low number of subjects and wide CIs.

Discussion

We investigated whether inflammatory markers are associated with levels of adiposity and whether inflammatory status and adiposity have combined effects on mortality in 90-year-old people. Our findings showed that in nonagenarians BMI and WC, but not WHR, were associated with levels of certain inflammatory markers, but the associations were different in men and women. Regarding the combined effects of adiposity and inflammatory status, the lowest mortality risk in women was in those participants who had low levels of WC or WHR combined with low inflammatory status. In men, the lowest mortality risk was in those participants who had high levels of BMI or WC combined with low inflammatory status.

On the basis of the cross-sectional analysis, IL-1RA was the most consistent marker associated with BMI and WC across genders. These positive associations are in line with the known positive association between IL-1RA and level of adiposity.[16] The fact that WHR was not associated with IL-1RA, or with any other inflammatory marker, suggests that

Table 3. Body Mass Index, Waist Circumference, and Waist-to-Hip Ratio Combined with Inflammatory Status: Effects on 4-Year Mortality in 90-Year-Old Women and Men

	Women (n = *157*)				*Men* (n = *53*)			
	N	*N (%) of subjects who died*	*Unadjusted*[a] *HR (95% CI)*	*Adjusted*[b] *HR (95% CI)*	N	*N (%) of subjects who died*	*Unadjusted*[a] *HR (95% CI)*	*Adjusted*[b] *HR (95% CI)*
BMI and inflammatory status								
Low BMI and low inflammation	47	16 (34.0)	1.00	1.00	13	11 (84.6)	1.00	1.00
Low BMI and high inflammaton	48	33 (68.8)	**2.47 (1.36–4.49)**	1.77 (0.93–3.38)	21	17 (81.0)	0.91 (0.43–1.96)	0.59 (0.22–1.54)
High BMI and low inflammation	16	7 (43.8)	1.43 (0.59–3.48)	1.81 (0.72–4.57)	6	2 (33.3)	0.25 (0.06–1.14)	**0.07 (0.01–0.51)**
High BMI and high inflammation	46	20 (43.5)	1.34 (0.69–2.58)	1.14 (0.58–2.24)	13	8 (61.5)	0.52 (0.21–1.29)	**0.31 (0.10–0.94)**
WC and inflammatory status								
Low WC and low inflammation	35	6 (17.1)	1.00	1.00	10	9 (90.0)	1.00	1.00
Low WC and high inflammaton	38	25 (65.8)	**5.60 (2.30–13.68)**	**5.63 (2.18–14.55)**	14	11 (78.6)	0.86 (0.36–2.10)	0.62 (0.19–1.95)
High WC and low inflammation	28	17 (60.7)	**5.56 (2.19–14.11)**	**7.23 (2.70–19.39)**	9	4 (44.4)	0.34 (0.10–1.11)	**0.13 (0.03–0.59)**
High WC and high inflammation	56	28 (50.0)	**3.58 (1.48–8.66)**	**2.73 (1.10–6.76)**	20	14 (70.0)	0.57 (0.24–1.32)	**0.25 (0.09–0.76)**
WHR and inflammatory status								
Low WHR and low inflammation	30	5 (16.7)	1.00	1.00	7	4 (57.1)	1.00	1.00
Low WHR and high inflammaton	35	21 (60.0)	**5.06 (1.91–13.44)**	**4.69 (1.64–13.46)**	15	11 (73.3)	1.82 (0.58–5.74)	1.24 (0.32–4.79)
High WHR and low inflammation	33	18 (54.5)	**4.95 (1.83–13.33)**	**4.57 (1.57–13.34)**	12	9 (75.0)	1.88 (0.58–6.14)	0.58 (0.14–2.42)
High WHR and high inflammation	59	32 (54.2)	**4.23 (1.65–10.86)**	**2.90 (1.08–7.73)**	19	14 (73.7)	1.44 (0.47–4.38)	0.48 (0.12–1.89)

Models represent Cox proportional hazards models with hazard ratios (HR) and 95% confidence intervals (95% CI).
Inflammatory status: C-reactive protein, interleukin-6, interleukin-1 receptor antagonist, and tumor necrosis factor-α taken into account.
Low inflammation: 0–1 inflammatory markers above the sex-specific median.
High inflammation: 2–4 inflammatory markers above the sex-specific median.
Cutpoint for BMI 25.00 kg/m^2. Sex-specific median cut point for WC (85 cm in women and 93 cm in men) and WHR (0.85 in women and 0.91 in men).
[a]Unadjusted univariate analyses.
[b]Each univariate model adjusted for history of diseases (cardiovascular disease, cancer, diabetes, respiratory disease, and infectious disease), functional status, and smoking.
CI, Confidence interval; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio.

in the oldest old population BMI and WC are more closely associated with level of adiposity than WHR. This finding is logical because high WHR may represent a relative lack of gluteal muscle mass in addition to a relative abundance of abdominal fat.[17]

BMI and WC were positively associated with CRP in women, whereas in men these associations were negative although nonsignificant. However, in men, the borderline significant association between CRP and BMI may partly explain our recent finding that mortality in normal-weight oldest old men is higher compared to overweight men.[14] It is possible that high CRP in oldest old men is more strongly associated with low BMI and malnutrition–inflammation–cachexia syndrome[18] than with high BMI. In general, levels of inflammatory factors are partly regulated by genes,[19,20] and they also are influenced by factors such as gender[21,22] and dietary patterns.[23,24] It is also important whether the adipose tissue is located viscerally or subcutaneously, because visceral adipose tissue is more metabolically active.[25] However, there is an ongoing debate regarding whether CRP is an actual risk factor for diseases or merely a marker of inflammation[26,27]; *i.e.*, whether CRP has a causal link to diseases.

In the longitudinal analyses, high inflammation was associated with higher mortality risk in women who had low WC or WHR, as could be expected. On the contrary, in men who had low level of adiposity, inflammatory status made no difference in mortality, and death rate was highest for men with low BMI or WC and low inflammation. In both low- and high-inflammation groups, women with high WC or WHR had significantly higher mortality risk, whereas men with high WC or BMI had significantly lower mortality risk compared to the reference group, respectively. These gender differences might be related to the fact that women have a higher fat percentage than men in general.[28] Regarding inflammation, experimental data has also demonstrated that under certain conditions, production of proinflammatory cytokines can initiate activation of a prosurvival cardioprotective pathway.[29] The fact that the results both in men and women remained similar after excluding the first 2 years of the follow-up suggests that reverse causality, *i.e.*, illnesses causing mortality early in the follow-up, is not causing the results. However, in women, reverse causality may well explain the results concerning WHR.

A wealth of data has demonstrated a phenomenon known as the obesity paradox, meaning that obesity has protective effects on mortality.[30–32] However, recent studies have shown that the obesity paradox, at least in part, can be explained by factors such as cardiorespiratory fitness,[33,34] adipocyte and adipose tissue abnormalities,[35] or persistent organic pollutants.[36] The findings of this study also shed light for the paradox in very old women, because low WC and WHR, when combined with low inflammatory status, were associated with particularly low mortality. The same direction of association was also seen in BMI, although to a lesser extent. In contrast, in men the results give further support for the obesity paradox, because higher values in BMI and WC had a protective effect on mortality regardless of the inflammatory status. Also, in a recent study by Clark et al., both high WC and high BMI were independently associated with better survival in a cohort of heart failure patients.[37] Similarly, in a recent systematic review of the literature, BMI was inversely associated with mortality risk, but, conversely, central obesity was directly associated with mortality risk.[38]

Interestingly women with high WC and low inflammation had roughly three times higher mortality risk than women with both high WC and inflammation. It could be speculated that as WC correlates positively with inflammatory markers, a high level of adiposity combined with low inflammatory status relates to ill health in women. The result might also reflect an *ex vivo* finding that the capacity to generate a proinflammatory immune response is predictive of long-term survival in the oldest old.[39]

The study has some major limitations. First, this very old cohort has obviously experienced a high selective mortality, and the results may not apply to younger age groups. Also, only half of the basic population was included, and the study sample is likely to be healthier than the whole age group. Second, the sample size was quite small, and particularly the number of men was low. Consequently the statistical power in men in the mortality analyses was very low. However, we considered it important to include men in the analyses as a separate group because earlier findings are scarce and the results clearly differed between the genders. In addition, the participants were mostly normal weight and overweight, thus the effects of obesity or very low weight combined with inflammation could not be examined. Finally, the mortality risks are likely to vary depending on how many inflammatory markers have an elevated level and where the cut-point for low and high inflammation is set. Due to small sample size, we could not explore these effects more closely. In all, our findings need to be confirmed with a larger study sample.

In conclusion, BMI and WC, but not WHR, are associated with some inflammatory markers in the oldest old, but the results differ in men and women. The findings give novel insight on the combined effects of adiposity and inflammatory status on mortality in the oldest old. In women, low WC or WHR combined with low inflammatory status gives clear survival benefit, whereas in men the survival benefit seems to be greatest in those with high WC or BMI combined with low inflammatory status. The gender differences and the interaction between inflammatory status and adiposity should be noted in future studies.

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Author Disclosure Statement

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