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The association of multidimensional frailty with metabolic syndrome and low-grade inflammation in community-dwelling older adults in the Netherlands: a Lifelines cohort study

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Abstract

Background Preventing metabolic syndrome (MetS) and frailty in older adults is crucial for healthy aging. The association between MetS and physical frailty is well-documented, with low-grade inflammation as potential explanation. However, the association between MetS and frailty as a multidimensional concept, and the association of low-grade inflammation with presence of MetS and frailty, is yet unclear. Therefore, we examined these associations low-grade inflammation in a large cohort of community-dwelling older adults.

Methods This cross-sectional study was performed among adults aged ≥ 65 years enrolled in the Dutch Lifelines population cohort. MetS was defined according to the Joint Interim Statement of 2009. Frailty was measured by the Groningen Frailty Indicator (GFI), which consists of 15 self-reported items on both physical and psychosocial functioning, with a score ≥ 4 indicating presence of frailty. The association between MetS and its five components and frailty was assessed using logistic regression models. Low-grade inflammation was represented by high-sensitivity C-reactive protein (hsCRP) level. The association of hsCRP level with presence of MetS and frailty was assessed using multinomial logistic regression in a sub-cohort with available hsCRP measurements.

Results Of 11,552 adults (52.1% women) included, the prevalences of MetS and frailty were 28% and 15%, respectively. MetS was positively associated with frailty after adjusting for relevant covariates (OR: 1.37; 95% CI: 1.22–1.53). MetS components elevated blood pressure was most strongly associated with frailty. In the sub-cohort of 3896 participants, high hsCRP was associated with presence of MetS and frailty (OR: 1.31; 95% CI: 1.15–1.51), and MetS alone (OR: 1.44; 95% CI: 1.33–1.56), but not to frailty alone. A higher hsCRP level was associated with a higher score on the physical domain of frailty (b: 0.06; 95% CI: 0.03–0.08).

Conclusions Presence of MetS is associated with presence of frailty indicated by a multidimensional index in a large group of Dutch older adults. Low-grade inflammation, indicated by plasma hsCRP level, was found to be associated

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with both presence of MetS and frailty and presence of MetS alone. Increased hsCRP levels were associated with the physical component of frailty, but not with frailty as a multidimensional concept.

Keywords Metabolic syndrome, Frailty, Groningen frailty indicator, Older adults, Healthy aging

Background

Due to improved standards of living and health care developments, life expectancy has doubled from approximately 40 years in the 19th century to around 80 years in current times [1, 2]. Along with the overall aging of the population, however, the burden of age-related disorders has increased as well. The parallel worldwide obesity pandemic has further contributed to a predominantly chronic disease burden, e.g., due to cardiovascular disease and diabetes, typically occurring at older age [3]. Obesity is associated with increased systemic inflammation as well as insulin resistance in the distal metabolic organs, which is directly linked to the development of metabolic syndrome (MetS) [4]. MetS encompasses a cluster of conditions, including central obesity, hypertension, insulin resistance and dyslipidemia, which collectively increases the risk of cardiovascular disease, as well as cardiovascular and all-cause mortality [5, 6]. Therefore, prevention and treatment of MetS is highly relevant for managing public health and health care resources in an aging, increasingly obese society.

Frailty is another critical condition to consider in the management of aging and chronic diseases. Frailty is a multidimensional concept and can be defined as 'a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, social, psychological) that are caused by the influence of a range of variables, which increases the risk of adverse outcomes' [7]. Incidence of frailty increases with higher age and adverse outcomes associated with frailty include an increased risk of hospital admissions, complications, increased healthcare costs, and mortality [8–13]. Therefore, it is important to prevent frailty or, if already present, to treat frailty at an early stage.

Inflammaging, i.e. 'a systemic state of chronic low-grade inflammation characterized by upregulated blood inflammatory markers', has been proposed as an underlying mechanism of frailty [14–16].

Low-grade inflammation can be identified by using a high sensitivity C-reactive protein (hsCRP) test. The hsCRP test can measure C-reactive protein (CRP) at much lower levels than the standard CRP test. Different studies have shown that inflammatory parameters, such as CRP are associated with frailty [17, 18]. However, it is still unclear whether this association with frailty is also visible if low-grade inflammation markers, such as hsCRP, are used. The presence of chronic low-grade inflammation may partially explain the association between MetS and physical frailty that has been described in previous literature, with a reported 50 to 80% higher odds of frailty in older adults with MetS [19–23].

Although frailty has been defined as a multidimensional concept, studies on MetS and frailty until now have been focusing on the physical aspects of frailty. Currently, it is unclear whether components of MetS are associated with frailty as a multidimensional concept, also including social and psychological aspects of frailty. Furthermore, the association of hsCRP as a marker of low-grade inflammation with presence of MetS and multidimensional frailty has not yet been explored. If hsCRP is associated with presence of MetS and multidimensional frailty, the hsCRP test could provide a tool for further prevention refinement. This, in its turn, may contribute to an optimized policy for age-related diseases in an increasingly aging population. Therefore, the aim of this study was to evaluate the association between MetS and multidimensional frailty in a large population cohort of community-dwelling older adults, and to explore the association with hsCRP as a marker for low-grade inflammation in presence of MetS and multidimensional frailty.

Methods

Study population and participants

For this cross-sectional study, data of older adults (≥65 years of age) participating in the Lifelines Biobank cohort study was used. Lifelines is a multi-disciplinary prospective population-based cohort study, examining in a unique three-generation design the health and health-related behaviors of 167,729 persons living in the Northern Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. The Lifelines study was conducted according to the principles of the Declaration of Helsinki and approved by the Medical Ethics Committee of the Institutional Review Board of the University Medical Center Groningen, The Netherlands (2007/152). The Lifelines adult study population is largely representative of the adult population of the Northern Netherlands. A detailed description of the Lifelines study can be found elsewhere [24, 25]. Before the study entry, a signed informed consent form was obtained from each participant.

Comprehensive physical examinations, blood biobanking, and questionnaires were conducted during the general and follow-up Lifelines assessments. Frailty was

assessed in older adults aged 65 years and older. Of the 167,729 adult Lifelines participants, 12,879 were invited for assessment of frailty at baseline from 2009 to 2014. For evaluating the association between MetS and frailty, those with missing data on frailty or MetS were excluded from this study (n=1327), leaving 11,552 older adults from baseline assessment as cohort 1. For exploring the role of hsCRP as a marker for low-grade inflammation in presence of MetS and frailty, we further excluded those participants who were not randomly selected to be examined for hsCRP (n=7656) due to limited resources at Lifelines, resulting in 3896 participants that formed cohort 2 (Supplementary Figure S1).

Clinical measurements and medication use

Anthropometric measurements and blood pressure (BP) were measured by trained staff. Anthropometric measurements were performed without shoes. Body weight was measured to 0.1 kg by the SECA 761 scale (Seca GmbH, Hamburg, Germany); height was measured to 0.5 cm in Frankfort Plane position by the SECA 222 stadiometer (Seca GmbH, Hamburg, Germany), and the waist circumference (WC) was measured to 0.5 cm by the SECA 200 measuring tape (Seca GmbH, Hamburg, Germany) [23]. BP was measured by Dynamap PRO 100V2 (GE Healthcare, Freiburg, Germany); systolic and diastolic BP were measured ten times within ten minutes, and each of the average values of the last three readings were used as BP parameters [23].

For analyses of lipids and glucose, blood samples were drawn between 8:00 and 10:00 am after overnight fasting at every general assessment. Serum levels of high-density lipoprotein cholesterol (HDL-C) were measured with an enzymatic colorimetric method, and total triglycerides (TG) was measured with a colorimetric UV method, all on a Roche Modular P chemistry analyzer (Roche, Basel, Switzerland). Fasting plasma glucose (FPG) was measured using a hexokinase method. All biochemical measurements were performed in singles. The hsCRP test was performed using CardioPhase hsCRP kit supplied by Siemens (BNII). Subsequently, the hsCRP level was categorized into <1.0 mg/L, 1.0–3.0 mg/L, and >3.0 mg/L [26]. Drug treatment for hypertension included medications with ATC codes C02 (antihypertensives), C03 (diuretics), C07 (beta-blocking agents), C08 (calcium channel blockers), and C09 (agents acting on the renin-angiotensin system), while drug treatment for elevated glucose included medications with ATC codes A10A (insulins and analogues) and A10B (oral blood glucose-lowering drugs).

Assessment of metabolic syndrome (MetS)

MetS was defined according to the Joint Interim Statement (JIS) of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity in 2009 [24]. The presence of at least three of the following five risk factors constitutes a diagnosis of MetS: (1) abdominal obesity (Europid): ≥ 94 cm in males and ≥ 80 cm in females; (2) elevated triglycerides: TG≥150 mg/dl (1.7 mmol/l); (3) reduced HDL-C: <40 mg/dL (1.0 mmol/L) in males and <50 mg/dL (1.3 mmol/L) in females; (4) elevated BP: systolic≥130 and/or diastolic≥85 mm Hg or drug treatment for hypertension; (5) elevated FPG: ≥ 100 mg/dl (5.6 mmol/l) or drug treatment of elevated glucose [27].

Assessment of frailty

Frailty was determined with the Groningen Frailty Indicator (GFI), which is recommended in the Dutch paramedic guideline for frailty in older adults [28] and was previously studied for measuring properties and construct validity in the Lifelines study population [29, 30]. The GFI is a 15-item survey that determines the level of multidimensional frailty in older adults, it measures the loss of functions and resources in both physical, cognitive, and sociopsychological domains [29]. All answer categories were dichotomized and a score of 1 indicates a problem or dependency. The range of the GFI total score is therefore 0 to 15, with a score of 4 or higher representing frailty [31]. Moreover, the first 9 items of GFI are considered an indicator of physical frailty [32]. The complete GFI survey and categorization of the answers can be found in Supplementary Table S1.

Other covariates

Relevant data on socio-demographic variables (age, sex, educational level, living situation), as well as lifestyle behaviors (smoking, physical activity, sleep duration, alcohol consumption, overall diet quality) and co-morbidities (presence of chronic kidney disease (CKD), lung disease, stroke and cancer history) were included in this study, to describe the study population and include as potential confounders in the statistical analyses, considering their known association with MetS, frailty or both [33–43]. Age and sex were recorded at baseline assessment. The highest educational level achieved was categorized as: [1] low—junior general secondary education or lower [International Standard Classification of Education (ISCED) level 0, 1 or 2]; [2] middle—secondary vocational education and senior general secondary education (ISCED level 3 or 4); and [3] high—higher vocational education or university (ISCED level 5 or 6) [44]. Smoking status was categorized into never, former and current smoker. Living conditions were self-reported and were categorized as living alone or not.

Non-occupational moderate-to-vigorous physical activity (MVPA) was calculated in minutes per week from the validated Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) data, which incorporated leisure-time and commuting physical activities, including sports, at moderate [4.0–6.4 metabolic equivalent of task (MET)] to vigorous (≥6.5 MET) intensity [45]. Sleep time was reported in hours per day. Dietary intake and alcohol intake over the past month were assessed using a validated 110-item semi-quantitative food frequency questionnaire (FFQ) that was developed by Wageningen University & Research [46]. The Lifelines Diet Score (LLDS) was calculated to assess the overall diet quality based on the FFQ. The LLDS ranks the relative intake of nine food groups with positive health effects (vegetables, fruit, whole-grain products, legumes/nuts, fish, oils/soft margarines, unsweetened dairy, coffee and tea) and three food groups with negative health effects (red/processed meat, butter/hard margarines and sugar-sweetened beverages). The development of this score is described in detail elsewhere [47]. CKD was considered present if estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2, or eGFR ≥ 60 ml/min/1.73 m2 and albumin-to-creatinine ratio (ACR) > 30 mg/g. Stroke was defined as self-reported history of stroke as well as use of the following types of medications: carbasalate calcium, acetylsalicylic acid, clopidogrel, vitamin K antagonists, and statins. Cancer history was considered present if the history of any type of cancer was self-reported. Lung disease was considered present if any of the following diseases was present: chronic obstructive pulmonary disease, asthma, and chronic mucus hypersecretion.

Statistical analyses

Participants' characteristics were presented as mean ± SD (Standard Deviation) for normally distributed data, median (IQR (interquartile range)) for non-normally distributed data, or frequencies n (%) for nominal variables. These characteristics were provided for the total study population in cohort 1 and across MetS status, and total population of cohort 2 and across the coexistence of MetS and frailty.

In cohort 1, associations of MetS and the five components of MetS with frailty, total GFI score, and physical GFI score were estimated by binary logistic regression and linear regression models, respectively. Regression results were shown as odds ratios (ORs) and beta coefficient (b) with 95% confidence intervals with p-values, respectively; all models were adjusted in a four-step manner: with model 1 adjusted for age and sex; model 2 further adjusted for education attainment and living conditions; model 3 further adjusted for relevant lifestyle behaviors (smoking status, sleep duration, non-occupational MVPA, alcohol consumption, and LLDS); model 4 further adjusted for comorbidities including stroke, lung diseases, cancer and CKD.

In cohort 2, the plasma level hsCRP was log-transferred to ensure normality. First, multinomial logistical regression models were used to investigate the associations of hsCRP with presence of MetS and frailty, with the group without MetS and Frailty as reference group. Regression results were shown as relative risk ratios (RRRs) with 95% confidence intervals with p-values and all models were adjusted in a four-step manner: with model 1 adjusted for age and sex; model 2 further adjusted for educational level and living conditions; model 3 further adjusted for relevant lifestyle behaviors (smoking status, sleep duration, non-occupational MVPA, alcohol consumption, and LLDS); model 4 further adjusted for comorbidities including stroke, lung diseases, cancer and CKD. Second, the association of hsCRP with MetS and its components were estimated using binary logistic regressions with the same four-step adjustment manner mentioned above. Third, the associations of hsCRP with prevalent frailty, total GFI score and physical GFI score were estimated by binary logistic regression and linear regression models, respectively. Regression results were shown as ORs or b with 95% confidence intervals with p-values and all models were adjusted in a five-step manner: with model 1 adjusted for age and sex; model 2 further adjusted for education attainment and living condition; model 3 further adjusted for relevant lifestyle behaviors (smoking status, sleep duration, non-occupational MVPA, alcohol consumption, and LLDS); model 4 further adjusted for comorbidities including stroke, cancer, CKD, and lung diseases; model 5 further adjusted for the presence of MetS. A mediation analysis with hsCRP as a mediator in the association between MetS and prevalent frailty, total GFI score and physical GFI score were conducted if the assumption of associations were met.

For all regression models, missing data on covariates were imputed using 20-fold multiple imputation with chained regression, given the missing at random patterns for the covariates. A statistical significance can be inferred when p-values ≤ 0.05. Effect of modification of age and sex were also explored for all models. All statistical analyses were conducted using Stata/MP 18.0 (StataCorp LLC, Texas, USA).

Results

In cohort 1, 3259 (28.2%) study participants met criteria for MetS; among them, 97.6% were at risk of abdominal obesity, 49.0% elevated TG, 43.7% reduced HDL-C, 85.9% elevated BP, and 69.7% elevated FPG. Frailty was prevalent in 15.1% of the study participants overall, 18.7% among individuals with MetS and 13.7% among individuals without MetS, respectively (Table 1). Participants with MetS were more likely to be male, current and former

Table 1 Participants characteristics of cohort 1

	Total population	MetS	Non-MetS	
Participants, n (%)	***n* = 11,552**	***n* = 3259 (28.2%)**	***n* = 8293 (71.8%)**	**p**
Frailty (GFI), n (%)				
Frail (GFI > = 4)	1747 (15.1)	608 (18.7)	1139 (13.7)	< 0.001
Non-frail (GFI < 4)	9805 (84.9)	2651 (81.3)	7154 (86.3)	
GFI-score, median (IQR)	1 (0–3)	1 (1–3)	1 (0–2)	< 0.001
Physical GFI-score, median (IQR)	0 (0–1)	1 (0–1)	0 (0–1)	< 0.001
MetS components, n (%)				
Abdominal obesity (Europids)				
yes	9067 (78.5)	3181 (97.6)	5886 (71.0)	< 0.001
no	2485 (21.5)	78 (2.4)	2407 (29.0)	
Elevated TG				
yes	2039 (17.7)	1598 (49.0)	441 (5.3)	< 0.001
no	9513 (82.3)	1661 (51.0)	7852 (94.7)	
Reduced HDL-C				
yes	1664 (14.4)	1424 (43.7)	240 (2.9)	< 0.001
no	9888 (85.6)	1835 (56.3)	8053 (97.1)	
Elevated BP				
yes	5841 (50.6)	2801 (85.9)	3040 (36.7)	< 0.001
no	5711 (49.4)	458 (14.1)	5253 (63.3)	
Elevated FPG				
yes	3320 (28.7)	2271 (69.7)	1049 (12.6)	< 0.001
no	8232 (71.3)	988 (30.3)	7244 (87.4)	
Age range, range	65–94	65–94	65–93	
65–75, %	84.9	82.6	85.9	< 0.001
75–85, %	14.2	16.2	13.4	
>=85, %	0.9	1.2	0.7	
Female, %	52.1	47.3	54.0	
BMI, kg/m2 mean ± SD	27.0 ± 3.9	29.2 ± 3.9	26.1 ± 3.4	< 0.001
Education, %				
low	53.9	59.6	51.7	< 0.001
middle	23.3	23.0	23.4	
high	22.8	17.4	24.9	
Living alone, yes%	16.4	16.3	16.5	0.8
Smoking status, %				
current	8.7	10.3	8.2	< 0.001
former	54.7	56.9	53.8	
never	36.6	32.8	38.0	
MVPA, min/wk	240 (115–480)	210 (60–440)	270 (120–510)	< 0.001
< 150 min/week, %	32.2	38.3	29.8	< 0.001
Sleep duration, hours/day	7.6 ± 1.0	7.7 ± 1.04	7.6 ± 0.98	< 0.001
Alcohol consumption, gram/day	5.09 (0.7–12.1)	3.35 (0.01–11.9)	5.8 (0.86–12.08)	< 0.001
LLDS, mean ± SD	26.7 ± 5.7	25.8 ± 5.8	27.0 ± 5.7	< 0.001
Co-morbidities, %	47.0	79.9	34.0	< 0.001
Stroke	2.1	3.2	1.6	< 0.001
Lung diseases	34.1	35.7	33.5	0.03
Cancer	14.0	14.4	13.8	0.3
CKD	2.1	4.0	1.3	< 0.001

*MetS: metabolic syndrome; GFI: Groningen frailty indicator; IQR: interquartile range; SD: standard deviation; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; BP: blood pressure; FPG: fasting plasma glucose; BMI: body mass index; MVPA: Non-occupational moderate-to-vigorous physical activity; LLDS: Lifelines diet score; CKD: chronic kidney disease

† Missingness of covariates: education (1.9%), living alone (0.8%), smoking status (0.5%), MVPA (8.2%), sleep duration (0.99%), alcohol consumption (2.3%); LLDS (2.3%)

‡ p indicates the comparison between the group with and without MetS

smoker, and less physically active; and had a lower education level and a higher BMI, more TV watching time, and poorer diet quality (Table 1). The group with both MetS and frailty had the highest average BMI, percentage of individuals with low education, the highest percentage of current smoker, and was least physically active (Table 2).

After adjusting for all covariates (Model 4, Table 3), participants with MetS had 37% higher odds of being frail than those without MetS (OR: 1.37; 95% CI: 1.22–1.53). When focused on each component of MetS, elevated BP (OR: 1.50; 95%CI: 1.35–1.68), reduced HDL-C (OR: 1.26; 95%CI: 1.09–1.46), and elevated FPG (OR: 1.23; 95%CI: 1.10–1.38) were significantly associated with prevalent frailty (Model 4, Table 3). In sensitivity analyses, presence of MetS was associated with a higher total GFI score (b: 0.37; 95% CI: 0.30–0.44). Participants with elevated TG, reduced HDL-C, elevated BP, and elevated FPG had 0.20 (95%CI: 0.12–0.28), 0.27 (95% CI: 0.19–0.36), 0.40 (95%CI: 0.34–0.46), and 0.23 (95%CI: 0.17–0.30) higher score of total GFI, respectively (Supplementary Table S2). The association magnitude between MetS and physical GFI (b: 0.35; 95%CI: 0.32–0.38) was comparable to the association between MetS and total GFI (Supplementary Table S3).

The participants' characteristics of cohort 2 are shown in Table 2. The median hsCRP levels were 2.0, 1.9, 1.3, and 1.2 mg/L in the MetS & frail, MetS & non-frail, non-MetS & frail, and non-MetS & non-frail groups,

Table 2 Participants characteristics of cohort 2

	Total population	MetS & Frail	MetS & Non-frail	Non-MetS & Frail	Non-MetS & Non-frail	
Participants, n (%)	*n* = 3896	*n* = 230 (5.9)	*n* = 952 (24.4)	*n* = 401 (10.3)	*N* = 2313 (59.4)	p
hsCRP, mg/L, median (IQR)	1.4 (0.8–2.9)	2.0 (1- 3.9)	1.9 (1-3.9)	1.3 (0.7–2.7)	1.2 (0.7–2.5)	< 0.001
< 1.0 mg/L, %	34.1	24.8	23.6	35.7	39.0	< 0.001
1.0–3.0 mg/L, %	42.1	41.7	44.	41.1	41.5	
> 3.0 mg/L, %	23.8	33.5	32.2	23.2	19.5	
GFI-score, median (IQR)	1 (0–3)	5 (4–6)	1 (0–2)	5 (4–6)	1 (0–2)	< 0.001
Physical GFI-score, median (IQR)	0 (0–1)	1 (1–2)	0 (0–1)	1 (0–2)	0 (0–0)	< 0.001
Age, years	70 ± 4	71 ± 5	70 ± 5	71 ± 5	69 ± 4	
65–75, %	84.1	77.4	81.9	80.0	86.3	< 0.001
75–85, %	15.1	20.4	17.2	17.5	13.3	
>=85, %	0.8	2.2	0.8	2.5	0.4	
Female, %	53.8	65.6	45.3	73.1	52.9	< 0.001
BMI, kg/m2 mean ± SD	27.1 ± 3.9	29.8 ± 4.2	29.1 ± 3.8	26.5 ± 4.1	26.2 ± 3.4	< 0.001
Education, %						
low	55.7	65.0	59.3	60.5	52.5	< 0.001
middle	23.9	24.2	24.1	21.8	24.1	
high	20.4	10.8	16.5	17.7	23.4	
Living alone, yes%	16.5	32.6	12.2	35.1	13.6	< 0.001
Smoking status, %						
current	10.0	15.3	12.5	10.7	8.3	< 0.001
former	53.6	46.7	54.1	52.5	54.2	
never	36.4	37.9	33.4	36.7	37.5	
MVPA, min/wk	240 (120–480)	180 (50–390)	240 (90–480)	240 (120–420)	270 (120–510)	< 0.001
< 150 min/week, %	31	41.9	34.6	30.4	28.4	< 0.001
Sleep duration, hours/day	7.6 ± 1.0	7.5 ± 1.4	7.7 ± 0.9	7.5 ± 1.2	7.6 ± 0.9	< 0.001
Alcohol consumption, gram/day	3.9 (0.69–11.7)	1.8 (0.003-11.0)	4.09 (0.30–12.4)	2.5 (0.007-9.0)	5.6 (0.96–11.7)	0.04
LLDS, mean ± SD	26.5 ± 5.6	25.8 ± 5.7	25.8 ± 5.7	26.6 ± 6.0	26.8 ± 5.5	< 0.001
	46.9	80.0	75.5	42.6	32.5	< 0.001
Co-morbidities, %						
Stroke	2.0	5.2	3.3	2.7	1.0	< 0.001
Lung diseases	43.4	44.3	43.5	48.6	42.3	0.1
Cancer	13.8	14.3	14.1	16.2	13.1	0.4
CKD	4.1	7.0	7.6	3.2	2.5	< 0.001

*MetS: metabolic syndrome; GFI: Groningen frailty indicator; IQR: interquartile range; SD: standard deviation; hsCRP: high-sensitivity C-reactive protein; BMI: body mass index; MVPA: Non-occupational moderate-to-vigorous physical activity; LLDS: Lifelines diet score; CKD: chronic kidney disease

† Missingness of covariates: education (2.9%), living alone (0.6%), smoking status (0.6%), MVPA (11.6%), sleep duration (0.5%), alcohol consumption (3.5%), LLDS (4.6%)

‡ p indicates the comparison among the groups with and without MetS/Frailty

Table 3 Logistic regression of MetS (Non-met as reference group) and components of MetS with prevalence of Frailty at baselines ($N = 11,552$)

	Model 1			Model 2			Model 3			Model 4		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
MetS	1.5	1.34–1.67	< 0.001	1.47	1.31–1.65	< 0.001	1.40	1.25–1.57	< 0.001	1.37	1.22–1.53	< 0.001
Components of MetS												
Abdominal obesity (Europids)	1.18	1.03–1.36	0.02	1.16	1.00–1.33	0.04	1.10	0.95–1.27	0.2	1.09	0.95–1.26	0.2
Raised TG	1.29	1.13–1.47	< 0.001	1.26	1.11–1.44	0.001	1.20	1.05–1.37	0.006	1.19	1.04–1.36	0.01
Reduced HDL-C	1.37	1.19–1.57	< 0.001	1.36	1.18–1.57	< 0.001	1.29	1.11–1.48	0.001	1.26	1.09–1.46	0.001
Elevated BP	1.57	1.41–1.74	< 0.001	1.57	1.41–1.74	< 0.001	1.54	1.38–1.72	< 0.001	1.50	1.35–1.68	< 0.001
Raised FPG	1.33	1.19–1.49	< 0.001	1.28	1.15–1.44	< 0.001	1.24	1.11–1.40	< 0.001	1.23	1.10–1.38	< 0.001

* Model 1 adjusted for age, sex; model 2, model 1 adjusted for education and living alone; model 3, model 2 adjusted for smoking status, MVPA < 150 min/week, sleep duration, alcohol consumption, and LLDS; model 4, model 3 adjusted for presence of stroke, cancer, CKD, and lung diseases

† MetS: metabolic syndrome; OR: odds ratio; CI: confidence interval; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; BP: blood pressure; FPG: fasting plasma glucose; MVPA: Non-occupational moderate-to-vigorous physical activity; LLDS: Lifelines diet score; CKD: chronic kidney disease

respectively. The proportion of participants with a high-risk level of hsCRP ≥ 3.0 mg/L was 33.5% in the MetS & frail group, 32.2% in the MetS & non-frail group, 23.2% in the non-MetS & frail group, and 19.5% in the non-MetS & non-frail group. After adjusting for covariates, individuals with an increased hsCRP level were more likely to be in the MetS & frail group over the non-MetS & non-frail group than the individuals with the lower hsCRP level (RRR: 1.31; 95% CI: 1.15–1.51) (Table 4, Model 4). Meanwhile, the increased hsCRP level was also associated with increased relative risk for being in the MetS & non-frail group relative to the non-MetS & non-frail group (RRR: 1.44; 95% CI: 1.33–1.56) (Table 4, Model 4). However, an increased hsCRP level was not associated with increased relative risk for being in the non-MetS & frail relative to the non-MetS & non-frail group (Table 4).

Further analyses on the association of hsCRP with physical GFI score and total GFI score showed that hsCRP level was positively associated with physical GFI score (b: 0.06; 95% CI: 0.03–0.08) (Model 4, Table 5). Further adjustment for presence of MetS attenuated the association magnitude slightly (b: 0.03; 95%CI: 0.01–0.06, Model 5, Table 5). An elevated hsCRP level was not significantly associated with a higher total GFI score or presence of frailty (Table 5). An elevated hsCRP was also associted with MetS and its components (Supplementary Table S5). As hsCRP was only associated with physical GFI, we have further conducted a mediation analysis with hsCRP as a mediator in the association between MetS and physical GFI. The mediation analysis showed that 3% of the association was mediated by hsCRP, indicating no substantial mediating role (Supplementary Figure S2). Age and sex did not modify the above associations (results not shown).

Discussion

In this study, we aimed to evaluate the association between MetS and multidimensional frailty and explore the association of hsCRP, as a marker for low-grade inflammation, with presence of Met and multidimensional frailty in a large cohort of community-dwelling older adults. We found that MetS and several components of MetS were associated with a multidimensional index of frailty. In addition, elevated hsCRP, as a marker for low-grade inflammation, was associated with presence of MetS and physical frailty, but not with frailty as a multidimensional concept in a sub-cohort of nearly 4000 older adults. Overall, older adults with MetS had a 37% higher odds of being frail, an elevated BP was associated with a 50% higher odds of being frail. In addition, having an increased hsCRP level was associated with higher odds of having MetS regardless of being frail or physically frail.

Table 4 Multinomial logistic regression of plasma hs-CRP (log-transferred) with co-existence of MetS and frailty ($N = 3896$)

	MetS & Frail			MetS & Non-frail			Non-MetS & Frail			Non-MetS & Non-frail
	RRR	95% CI	p	RRR	95% CI	p	RRR	95% CI	p	
Model 1	1.38	1.21–1.58	< 0.001	1.48	1.37–1.60	< 0.001	1.04	0.94–1.17	0.4	ref
Model 2	1.37	1.20–1.57	< 0.001	1.47	1.37–1.59	< 0.001	1.05	0.94–1.17	0.4	ref
Model 3	1.32	1.15–1.51	< 0.001	1.45	1.34–1.56	< 0.001	1.02	0.91–1.14	0.7	ref
Model 4	1.31	1.15–1.51	< 0.001	1.44	1.33–1.56	< 0.001	1.01	0.90–1.13	0.8	ref

* Model 1 adjusted for age, sex; model 2, model 1 adjusted for education and living alone; model 3, model 2 adjusted for smoking status, MVPA < 150 min/week, sleep duration, alcohol consumption, and LLDS; model 4, model 3 adjusted for stroke, cancer, CKD, and lung diseases

† hs-CRP: high-sensitivity C-reactive protein; MetS: metabolic syndrome; RRR: relative risk ratio; CI: confidence interval; MVPA: Non-occupational moderate-to-vigorous physical activity; LLDS: Lifelines diet score; CKD: chronic kidney disease

The association between MetS and multidimensional frailty in the current study corresponds to previous studies that studied the association of MetS with frailty [20–22]. However, these studies mainly focused on physical frailty. The current study appears to be the first large cohort study that confirmed the association of MetS with frailty measured as a multidimensional concept, including social and psychological aspects of frailty. Our study also demonstrates an association between elevated BP and elevated FPG, and multidimensional frailty. This is in line with other studies that showed that participants with combined MetS and physical frailty had a higher risk of cardiovascular disease, compared to individuals with MetS but without frailty [20, 48]. In addition, frailty was previously reported to be associated with a higher prevalence of MetS, raised FPG and an increased risk of diabetes [49, 50].

Several mechanisms have been proposed to elucidate the relationship between MetS and frailty, including a shared common pathway of chronic low-grade inflammation. However, to our knowledge, previous studies investigating MetS and frailty did not examine mechanisms related to factors such as hsCRP, a biomarker of low-grade inflammation status. Although hsCRP was not associated with frailty as a multidimensional concept, the present study indicates that chronic low-grade inflammation, as indicated by elevated level of hsCRP, is associated with both MetS and physical frailty. Our study therefore supports the hypothesis that chronic low-grade inflammation might partially explain the bidirectional link between MetS and physical frailty. Chronic low-grade inflammation has been described as part of the concept of immunosenescence, which refers to the aging of the immune system and may contribute to development and progression of several age-related diseases such as cardiovascular disease and type 2 diabetes [14, 15, 51]. Therefore, future studies should explore the value of biomarkers of immunosenescence to help detect and grade severity of MetS and frailty among older adults.

The findings of this study have several practical implications. Firstly, since MetS and frailty can be (partially) reversible [52, 53], early detection and management of MetS and frailty may allow for delay of development of MetS and frailty. Since the prevalence of MetS and frailty in our older adult population aged 65 years and above was notable (28% and 15%, respectively), there may be potential for lower burden for the healthcare system as a result of early detection and management of MetS and frailty. The results also show the potential of implementing the hsCRP test as a risk indicator in preventive risk profiles for older adults. The established relationship between elevated hsCRP and physical frailty, both of which are associated with an increased risk of type 2 diabetes and cardiovascular disease, suggests that including measurements of hsCRP in older adults could serve as a valuable marker for identifying chronic low-grade inflammation.

This study has several strengths. Firstly, the study sample included in this study was a large community-dwelling cohort of older adults that represents the population of the Northern Netherlands. This enhanced our statistical power, precision, and generalizability, compared to previous studies [21]. Secondly, the GFI determines the level of frailty as a multidimensional concept. Both the psychometric properties and content validity of the GFI have been tested in the Lifelines population and have proven to be adequate [54, 55]. As a result of measuring frailty as a multidimensional concept, our frailty assessment does not only include the physical domain but also the psychological and social domains. This approach helps to capture the complex nature of frailty, leaning to more accurate identification and better-informed policies and interventions. Thirdly, in the subgroup analysis (cohort 2), we were able to include hsCRP tests together with MetS and frailty assessment, which made it possible to explore part of the mechanism behind the association between MetS and multidimensional frailty. Finally, we were able to consider a broad range of socio-demographic and lifestyle factors as well as relevant co-morbidities as confounding and mediating variables in our statistical models to further increase the robustness of our results.

However, study limitations should also be acknowledged. Firstly, due to the cross-sectional design of this study, no causal inferences or order in the relationship between MetS and frailty could be established.

Table 5 Linear regression and binary logistic regression of plasma hs-CRP (log-transferred) with physical domain of GFI, total GFI score, and frailty ($N = 3896$)

	Model 1			Model 2			Model 3			Model 4			Model 5		
	b/OR	95% CI	p	b/OR	95% CI	p	b/OR	95% CI	p	b/OR	95% CI	p	b/OR	95% CI	p
Physical GFI	0.07	0.05–0.10	< 0.001	0.07	0.05–0.10	< 0.001	0.06	0.04–0.09	< 0.001	0.06	0.03–0.08	< 0.001	0.03	0.01–0.06	0.005
Total GFI	0.07	0.02–0.13	0.007	0.07	0.02–0.12	0.01	0.05	-0.005-0.10	0.08	0.04	-0.01-0.09	0.1	0.02	-0.03-0.07	0.5
Frailty (GFI > = 4)	1.03	0.95–1.12	0.4	1.03	0.94–1.12	0.5	1.00	0.92–1.09	0.9	1.00	0.91–1.09	0.9	0.97	0.89–1.07	0.6

* Model 1 adjusted for age, sex; model 2, model 1 adjusted for education and living alone; model 3, model 2 adjusted for smoking status, MVPA < 150 min/week, sleep duration, alcohol consumption, and LLDS; model 4, model 3 adjusted for stroke, cancer, CKD, and lung diseases; model 5, model 4 adjusted for presence of MetS

† hs-CRP: high-sensitivity C-reactive protein; GFI: Groningen frailty indicator; MetS: metabolic syndrome; OR: odds ratio; CI: confidence interval; MVPA: Non-occupational moderate-to-vigorous physical activity; LLDS: Lifelines diet score; CKD: chronic kidney disease

Nevertheless, due to the initial design of Lifelines cohort, the GFI was only sent to participants during baseline assessment and not in the follow-up assessments. Future prospective population data is therefore warranted to study the nature and direction of their relation further and unravel the mechanisms behind their associations. Secondly, the Lifelines population includes predominantly Caucasians, which limits the generalizability of our results to other ethnic groups. Third, to operationalize frailty, we included a cut-off score of four for the GFI based on previous studies [56], however, this cut-off might also include 'pre-frail' older adults, therefore, a sensitivity analysis using total GFI score as an ordinal response variable was included and comparable results were obtained (Supplementary Table S3). Furthermore, only 34% of participants from cohort 1 were included in cohort 2 due to the availability of hsCRP measurements, which could potentially yield selection bias. However, the characteristics of those with and without missing data on hsCRP were not substantially different and were mostly comparable (Supplementary Table S4), so we do not expect the influence of selection bias on our results from cohort 2.

Conclusions

In this large cohort of community-dwelling Dutch older adults, the presence of MetS was positively associated with being frail measured as a multidimensional concept. Additionally, we found that those with elevated plasma hsCRP levels were more likely to have MetS and be physically frail. Our results further confirmed that low-grade inflammation might be a potential marker for MetS and physical domain of frailty. Future prospective research should focus on the nature of the association between MetS and (multidimensional) frailty, and the role of low-grade inflammation therein. This could lead to more effective interventions and strategies for improving management of aging-related conditions.

Abbreviations

GFI	Groningen Frailty Indicator
MetS	Metabolic syndrome
ISCED	International Standard Classification of Education
FFQ	Food frequency questionnaire
LLDS	Lifelines diet score
MVPA	Non-occupational moderate-to-vigorous physical activity
SQUASH	Short QUestionnaire to ASsess Health-enhancing physical activity
MET	Metabolic equivalent of task
BMI	Body mass index
SD	Standard deviation
IQR	Interquartile range
OR	Odds ratio
CI	Confidence interval

Supplementary Information

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Supplementary Material 1

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Author contributions
Martine J. Sealy: Conceptualization, Investigation, Writing - Original Draft; Iris M. Y. van Vliet: Conceptualization, Investigation, Writing - Original Draft; Harriët Jager-Wittenaar: Conceptualization, Writing - Review & Editing; Gerjan J. Navis: Conceptualization, Writing - Review & Editing; Yinjie Zhu: Conceptualization, Formal analysis, Investigation, Writing - Original Draft, Visualization, Supervision, Project administration.

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Data availability
The data that support the findings of this study are available from Lifelines Biobank but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Lifeline Biobank. Any researchers can apply to use data from Lifelines Biobank, including the variables used in this investigation. Information about access to Lifelines data is given on their website: (https://www.lifelines-biobank.com/researchers/working-with-us/step-1-prepare-and-submit-your-application).

Declarations

Ethics approval and consent to participate
The Lifelines cohort study was conducted according to the principles of the Declaration of Helsinki and approved by the Medical Ethics Committee of the Institutional Review Board of the University Medical Center Groningen, The Netherlands (2007/152). Written informed consent was obtained from the participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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