Metabolic syndrome and insulin resistance are associated with frailty in older adults: a prospective cohort study

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Abstract

Background: diabetes increases the risk of frailty that is a leading cause of disability and premature mortality in older people. Metabolic syndrome (MS) and insulin resistance (IR) are strong risk factors for diabetes and could, thus, lead to frailty. However, the association between MS or IR and frailty has barely been investigated.
Methods: data were obtained from a cohort of 1,499 community-dwelling individuals aged ≥60, who were free of diabetes at 2008–10 and were followed up for 3.5 years. At baseline, MS was ascertained according to the harmonised definition, and IR with the Homoeostatic Model Assessment for IR index (HOMA-IR). Frailty was defined as having three or more of the Fried's criteria: exhaustion, low physical activity, slow walking, unintentional weight loss and low grip strength. Statistical analyses were performed with logistic regression, and adjusted for the main confounders.
Results: in 2012, 84 cases of incident frailty were identified. Compared with subjects without MS, those with MS showed increased risk of frailty (multivariate odds ratio [OR]: 1.85; 95% confidence interval [CI] 1.12–3.05). The association persisted after further adjustment for fibrinogen and C-reactive protein. When the frailty criteria were considered individually, low grip strength was the criterion that showed a stronger association with MS (OR: 1.67; 95% CI: 1.25–2.21). Higher HOMA-IR values were also associated with higher risk of frailty.
Conclusion: MS and IR were associated with increased risk of frailty. This work extends the spectrum of harmful consequences of MS, and suggests that preventing or controlling MS may serve to delay frailty.

Keywords: *Frailty, metabolic syndrome, insulin resistance, abdominal obesity, cohort study, older people.*

Introduction

Frailty is a geriatric multi-systemic syndrome characterised by sarcopenia and decreased functional reserve, which increases vulnerability even to minor external stressors. In recent years, this syndrome has attracted a lot of attention because it allows for identifying a subpopulation of older adults at a high risk of adverse health outcomes (e.g. recurrent hospitalisation, institutionalisation and premature death) [1], and because it represents an early step in the disablement process that is potentially reversible [2–4].

Diabetes mellitus is an important risk factor of frailty among older people [5]. Unhealthy behaviours, obesity, poor glucose control and altered serum lipid profile among diabetic patients partially explain this association [6]. Of

note is that diabetes is a severe metabolic disorder, that is seldom reversible. However, it is possible that a less severe condition such as the metabolic syndrome (MS) and insulin resistance (IR), which are strong risk factors for diabetes, could also lead to frailty. Furthermore, the association of MS and IR with frailty is plausible because they might share potential mediators. If the association under study were true, it would be of public health relevance because MS is very frequent (25% or more of the Spanish non-diabetic population aged ≥65 has MS) and is reversible through healthy behaviours [7].

The few studies that have assessed the association between MS and frailty have found inconsistent results: While a cross-sectional study showed a significant positive relationship between MS and frailty [8], a prospective

analysis of the Cardiovascular Healthy Study (CHS) only found a weak and not statistically significant association [9].

Accordingly, this paper has examined the association of MS and IR with the risk of frailty in a cohort of community-dwelling older adults in Spain; it also investigated if such association could be explained by biomarkers of thrombosis and inflammation.

Methods

Study design and participants

The Seniors-ENRICA is a cohort study whose methods have been reported previously [10]. The cohort was established between 2008 and 2010 with participants aged 60 and over. The information was collected in three stages: First, a telephone interview to collect data on lifestyle and morbidity; next, a home visit to obtain blood and urine samples and finally, a second home visit, to perform a physical examination and to assess regular food consumption. The participants were contacted again in 2012, after a mean follow-up of 3.5 years.

The study protocol was approved by the Ethics Committee of Clinical Research of 'La Paz' University Hospital in Madrid. All participants gave written informed consent.

Study variables

According to the harmonised definition [11], MS was defined as having at least three of the following five criteria: abdominal obesity (waist circumference ≥102 cm in men, or ≥88 cm in women); fasting blood glucose 100–126 mg/dl and not treated with antidiabetic drugs; high blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg) or receiving antihypertensive drugs; triglycerides ≥150 mg/dl and serum high-density lipoprotein (HDL) cholesterol <40 mg/dl in men or <50 mg/dl in women. See Supplementary data, Appendix 1, available at *Age and Ageing* online for a detailed description of measurement of MS components [7].

Frailty was assessed according to the definition proposed by Fried *et al.* in the CHS [2]. Specifically, frailty was defined as having at least three of the following five criteria: exhaustion, low physical activity, slowness, unintentional weight loss and low grip strength. See Supplementary data, Appendix 2, available at *Age and Ageing* online for a detailed description of frailty measurement.

We also used baseline data on potential confounders of the study association, that included socio-economic variables, lifestyle and morbidity. See Supplementary data, Appendix 3, available at *Age and Ageing* online for a detailed description of these variables. Moreover, two cardiometabolic biomarkers were considered as potential mediators of the study association: fibrinogen that was measured with the coagulation method, and high sensitivity C-reactive protein (Hs-CRP) that was assessed by latex-enhanced nephelometry.

Lastly, insulin was determined by immunoradiometric assay. The Homoeostatic Model Assessment for IR index (HOMA-IR) was calculated by multiplying glucose in mg/dl by insulin in mU/l and dividing by 405 [12].

Statistical analysis

From the 2,519 cohort participants alive in 2012, 154 lacked data on frailty at baseline and 412 at follow-up. Of the remaining 1,953 individuals, we excluded 42 with frailty at baseline, 36 with incomplete information on MS, and 26 with missing data on potential confounders. Finally, we excluded 278 subjects with diabetes (glucose ≥126 mg/dl or treated with antidiabetic drugs), and 72 with cardiovascular disease (myocardial infarction, stroke or heart failure) at baseline, to make sure that the assessed associations are not due to the strong link between MS and these diseases. Therefore, the analyses were performed with 1,499 individuals.

The association between MS and frailty was summarised with odds ratios (ORs) and their 95% confidence interval (CI), obtained from logistic regression. Three logistic models with progressive adjustments for covariates were built. Model 1 adjusted for sex, age and education. Model 2 further adjusted for lifestyle and morbidity. And the third model, intended for assessing potential mediators, additionally adjusted for fibrinogen and Hs-CRP. Finally, detailed associations between MS, or its components, and each one of the frailty criteria were assessed among the participants who were robust (without any frailty criteria) at baseline. These analyses were adjusted as in Model 2.

Given that baseline waist circumference is a component of MS, and that weight loss during follow-up could simply reflect regression to the mean, as a sensitivity analysis we estimated the association after excluding the unintentional weight loss criterion from the definition of frailty; thus, those meeting ≥2 out of the 4 remaining Fried criteria were considered frail.

Natural splines were used to explore the dose-response association between HOMA-IR and frailty without assuming any pre-specified relationship. The 20th percentile was used as a reference. These spline models were adjusted for all covariates as in Model 2.

A two-sided P-value < 0.05 was considered statistically significant. The analyses were performed in Stata v13 (Stata Corp L.P, College Station, TX).

Results

At baseline, 462 (30.8%) study participants had MS; among them, 85.9% had abdominal obesity, 67.9% high blood glucose, 91.3% elevated blood pressure, 47.1% high triglycerides and 49.7% low HDL-cholesterol. See Supplementary

data, Appendix 4, available at *Age and Ageing* online for a table comparing the baseline characteristics of individuals with and without MS.

After a 3.5 year follow-up, 84 cases of incident frailty were identified. After adjusting for socio-economic variables, healthy behaviours, and morbidity (Model 2, Table 1), participants with MS had a higher risk of frailty than those without MS (OR: 1.85; 95% CI: 1.12–3.05). The association did not decrease substantially after adjusting for fibrinogen and Hs-CRP, which would happen if they were important mediators of this association (Model 3, Table 1). The results also persisted when the criterion of unintentional weight loss was excluded (data not shown).

When we focused on each component of MS, abdominal obesity was the single one showing a statistically significant association with increased frailty risk (OR: 2.14; 95% CI: 1.19–3.84) (Model 2, Table 1). The rest of the components, except high blood pressure, presented a tendency to a higher risk of frailty, but did not achieve statistical significance (Table 1). We reran the analyses excluding abdominal obesity, thus MS was defined as having at least two of the remaining four components; in this case the OR (95% CI) of frailty associated with MS was 1.52 (0.96–2.42) in Model 1, and 1.32 (0.79–2.18) in Model 3.

Regarding each frailty criterion, low grip strength was the one with the strongest association with MS (OR: 1.67; 95% CI: 1.25–2.21). When we investigated the association of each component of MS with each frailty criterion, abdominal obesity was linked to exhaustion, and low grip strength. High triglycerides and low HDL-cholesterol were linked to unintentional weight loss (Table 2).

Finally, in this sample of non-diabetic participants, HOMA-IR and incident frailty showed a positive association for HOMA-IR values above two, which became statistically significant above four; similarly, high values of HOMA-IR were significantly associated with exhaustion, unintentional weight loss and low grip strength (Figure 1). Finally, the OR (95% CI) of frailty associated with a one-point increase in HOMA-IR was 1.15 (1.01–1.32).

Discussion

In this cohort of community-dwelling older adults free from diabetes and cardiovascular disease at baseline, MS and IR were associated with increased risk of frailty, and the former association was mostly due to the role of abdominal obesity. Also MS showed a direct association with low grip strength. Moreover, these findings were not explained by plasma fibrinogen or serum Hs-CRP.

Our results are in line with two recent cross-sectional studies assessing the association between MS and frailty. In the first one, conducted among 118 subjects with mean age of 76 years, those with MS showed a 53% higher frequency of frailty than those without MS [8]. In this study, MS was also linked to exhaustion, slow gait and reduced grip strength. Likewise, in the second study among 1,971 functionally independent individuals in Japan older than 65,

MS was associated with higher frequency of sarcopenia, defined as the presence of low muscle mass plus the presence of either low muscle strength or low physical performance [13]. The association was strong, and abdominal obesity was the main contributor to the association across sex and age groups.

By contrast, in the prospective CHS, Barzilay *et al.* [9] found no association between MS and frailty. We do not know the reasons for the inconsistent results between our study and the CHS, but one possible reason is that participants in the CHS were older than in our study (mean age of 72 versus 68) and it is well established that the effect of cardiovascular risk factors on health outcomes tend to decrease with age [14]. On the other hand, similarities in both studies were that blood pressure was not associated with frailty and that HOMA-IR did show a positive association.

Concerning IR, some authors consider that it is simply one more component of MS [9, 15], while for others it plays a central pathogenic role in MS [16]. Our results are consistent with previous literature in showing that IR is associated with frailty [9, 17] especially among those with abdominal obesity [18]. One mechanism of this association is that the decline in insulin sensitivity causes an imbalance toward muscle mass catabolism resulting in sarcopenia and loss of strength [17, 19].

There is some evidence of the association of the different MS components with frailty; in some cross-sectional studies, abdominal obesity [20–23], high blood glucose [23], high blood pressure [22, 23], high triglycerides [23] and low HDL-cholesterol [22, 23], have been linked to a higher frequency of frailty. Of note is that while IR was associated with frailty in our study, high glucose only showed a tendency to increase frailty risk. It could be due to the fact that individuals with diabetes at baseline were excluded from the analyses, so we only assessed the association among those with glucose ≤126 mg/dl; moreover, in this situation, IR is a more sensitive marker of altered glucose metabolism than glucose levels. Lastly, and in contrast to our results, in one longitudinal analysis of the CHS those individuals with hypertension had a significantly greater decline in gait speed [22].

The physiopathological mechanisms of frailty syndrome are not completely understood, but they may include chronic low-grade inflammation, a prothrombotic state, oxidation and increased IR [24, 25]. These biological processes are altered in individuals with MS [21, 26]. Thus, Hs-CRP, interleukins, tumour necrosis factor alpha, clotting factors and oxidative protein damage have been linked to both MS and frailty [27, 28]. However, the extent to which each of these mechanisms explains the association between MS and the risk of frailty is uncertain. According to our analysis, an unspecific inflammatory marker (Hs-CRP) and a thrombotic marker (fibrinogen) do not substantially explain the association between MS and frailty. This could be partially due to the fact that the analyses were adjusted for comorbidity (e.g. musculoskeletal disease or chronic

Table 1. ORs (95% CI) of frailty risk according to MS and its components ($N = 1,499$)

	Model 1	Model 2	Model 3
MS	2.25 (1.41–3.60)*	1.85 (1.12–3.05)*	1.81 (1.08–3.03)*
Component of the MS			
Abdominal obesity[a]	2.57 (1.48–4.47)*	2.14 (1.19–3.84)*	2.04 (1.12–3.70)*
High blood glucose[b]	1.45 (0.89–2.35)	1.24 (0.74–2.08)	1.27 (0.75–2.17)
Blood pressure ≥130/85 mm Hg	0.88 (0.50–1.56)	0.90 (0.49–1.63)	0.89 (0.48–1.66)
Triglycerides ≥150 mg/dl	2.04 (1.17–3.55)*	1.70 (0.93–3.10)	1.71 (0.94–3.26)
Low HDL-cholesterol[c]	1.21 (0.71–2.07)	1.08 (0.61–1.91)	0.94 (0.51–1.71)

[a]Abdominal obesity: waist circumference ≥102 cm in men, and ≥88 cm in women.
[b]Fasting blood glucose 100–126 mg/dl.
[c]HDL-cholesterol level <40 mg/dl in men or < 50 mg/dl in women.
*$P < 0.05$.
Model 1: Adjusted for sex, age, educational level (no formal or primary education, secondary education, university).
Model 2: As Model 1 and additional adjustment for Mediterranean Diet Adherence Screener adherence ≥ 9, tobacco consumption (never smokers, former smokers, current smokers), alcohol consumption (never drinker, former drinker, moderate drinker, excessive drinker), leisure time physical activity METs-h/week (quartiles), time spent on watching television h/week (quartiles), total energy intake kcal/day (quartiles), asthma or chronic bronchitis, cancer, depression and musculoskeletal disease.
Model 3: As Model 2 and additional adjustment for fibrinogen and Hs-CRP.

Table 2. ORs (95% CI) of each frailty criterion according to MS and its components among robust participants ($n = 1,246$)

	Exhaustion	Low physical activity	Slow walking	Unintentional weight loss	Low grip strength
MS	1.03 (0.64–1.63)	1.34 (0.93–1.94)	0.89 (0.61–1.28)	1.17 (0.70–1.95)	1.67 (1.25–2.21)*
Abdominal obesity[a]	1.62 (1.03–2.54)*	1.34 (0.93–1.92)	1.06 (0.76–1.46)	1.43 (0.91–2.24)	1.63 (1.26–2.11)*
High blood glucose[b]	1.02 (0.63–1.62)	1.25 (0.88–1.87)	1.13 (0.76–1.66)	1.35 (0.87–2.10)	1.00 (0.77–1.31)
Blood pressure ≥130/85 mmHg	0.78 (0.48–1.27)	0.96 (0.64–1.44)	0.86 (0.56–1.31)	1.00 (0.57–1.75)	0.91 (0.66–1.26)
Triglycerides ≥150 mg/dl	1.47 (0.85–2.54)	1.09 (0.69–1.71)	0.69 (0.40–1.19)	2.73 (1.58–4.72)*	1.25 (0.86–1.79)
Low HDL-cholesterol[c]	0.86 (0.50–1.49)	1.15 (0.75–1.75)	0.85 (0.53–1.36)	1.87 (1.09–3.20)*	1.18 (0.84–1.66)

[a]Abdominal obesity: waist circumference ≥102 cm in men, and ≥88 cm in women.
[b]Fasting blood glucose 100–126 mg/dl.
[c]HDL-cholesterol level <40 mg/dl in men or <50 mg/dl in women.
*$P < 0.05$.
Adjustments as in Model 2 in Table 1.

respiratory disease) linked to low-grade chronic inflammation. On the other hand, our study found that IR was associated with frailty, coinciding with the results from Barzilay *et al.* [9].

There were some limitations in our study. First, the number of incident cases of frailty was small, so statistical significance was not achieved in relative large associations such as that of triglycerides and frailty (OR: 1.71; Table 2). Second, this was a cohort of relatively young and non-institutionalised older adults. Thus, results might not apply to the oldest old or in other settings. Third, the duration of follow-up was only 3.5 years, that might not allow for observing the full impact of MS on frailty. However, frailty is a rather frequent outcome and the relatively short life expectancy of older adults makes of particular interest to reveal short-term effects of both risk factors and preventive interventions. Fourth, we did not assess the severity of morbidity; thus, despite the analyses were adjusted for morbidity and a good number of covariates, we cannot rule out a certain degree of residual confounding. Fifth, Models 2 and 3 have a large number of covariates compared to the

number of incident cases of frailty, but results were robust because they did not change much from Model 1 (adjusted only for three variables) to Models 2 and 3. Lastly, we acknowledge that MS has been the subject of substantial criticism mostly because this syndrome as a whole does not seem to predict cardiovascular disease better than the sum of its individual components. However, cardiovascular risk factors are usually clustered, and the diagnosis of MS may help to identify high-risk patients who could benefit from appropriate lifestyle interventions [29]. This study also had some strengths, which include the prospective design and the use of standardised procedures and validated instruments for the physical exam and biological determinations.

In conclusion, this work extends the spectrum of harmful consequences of MS in older people, and has important practical implications. Given that frailty does not habitually reverse spontaneously, and that both MS and frailty could be controlled or prevented by a healthy lifestyle, our results emphasise the need of specific intervention focusing on healthy behaviours. These behaviours may include weight control, aerobic physical activity and endurance exercises, as
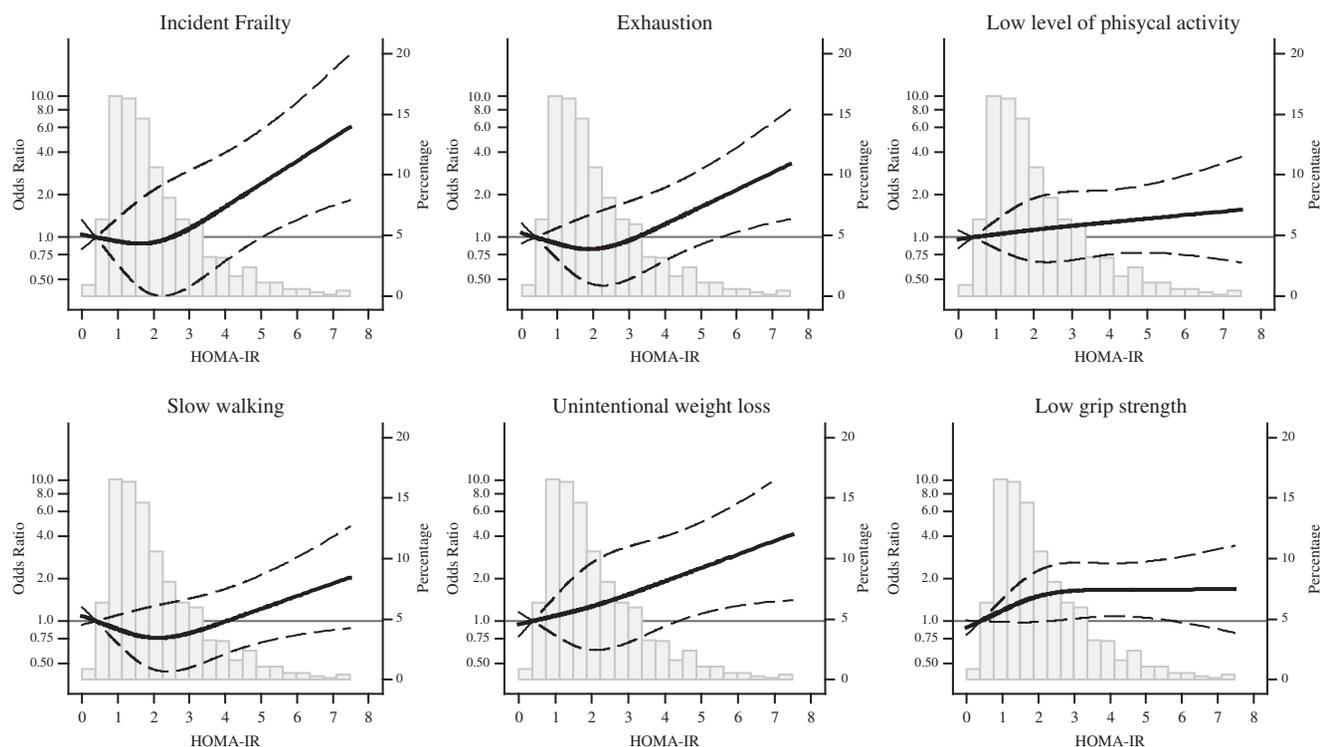
Figure 1. Dose-response association between HOMA-IR, frailty and each frailty criterion in older adults (n = 1,499). The 20th percentile was used as reference. Analyses were adjusted as in Model 2 in Table 1.

well as a healthy diet (e.g. Mediterranean diet),[10] rich in fruit and vegetables, olive oil (rich in monounsaturated fat) and with sufficient protein intake. Future research should establish the specific mechanisms of the association between MS and frailty, and examine the role of body composition (fat distribution) on this association.

Key points

- Metabolic syndrome (MS) and insulin resistance (IR) are strong risk factors for diabetes and, like diabetes, could lead to frailty.
- MS and IR showed increased risk of frailty that was mostly due to the role of abdominal obesity.
- These associations were not explained by fibrinogen or Hs-CRP.

Supplementary data

Supplementary data are available at *Age and Ageing* online.

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