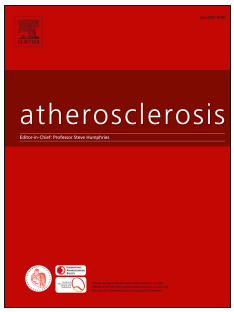

Association between serum ferritin and acute coronary heart disease: A population-based cohort study

Carlen Reyes, Nuria Aranda Pons, Cristina Rey Reñones, Josep Basora Gallisà, Victoria Arija Val, Cristian Tebé, Gemma Flores Mateo

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Author contributions section

All authors have contributed to the study according to international consensus on authorship and have approved the final draft, agreeing with the analyses of the data and the conclusions reached in the manuscript. CR wrote the first draft of the manuscript. GFM conceived and designed the study. NAP, CRR, JBG, VAV supervised the analysis, edited the manuscript and contributed to the discussion.

Best regards,

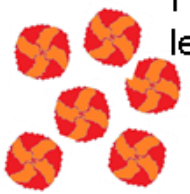
Gemma Flores Mateo

COHORT

N = 242,084 subjects

Inclusion criteria

- Subjects aged between 35 and 74 years
- Serum ferritin at baseline
- Without any know cardiovascular disease



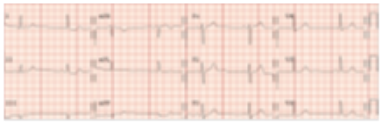
Ferritin levels

OUTCOMES

ICD-10 codes
I21,I210-I219, I22,
I220-I240, I241, I248
and I249

RESULTS

High levels of serum ferritin does not confer an increased risk of Coronary Heart Disease in Mediterranean area



Follow-up 8.4 years

1,106 incident cases of CHD

Association between serum ferritin and acute coronary heart disease: A population-based cohort study

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Summary

Background and aims Several studies aiming to determine the association between iron stores and the coronary heart disease (CHD) have reported conflictive results. None of them has been performed in a Mediterranean region. Our aim is to assess the association between the level of serum ferritin and the incidence of CHD in a Mediterranean region.

Methods. We performed a cohort study using a primary health care population database. Primary outcome was incidence of CHD. Subjects aged between 35 and 74 years with serum ferritin (SF) measurements at baseline (January 1, 2006 to December 31, 2008) were included. Cox regression models were used to compute hazard ratios (HRs) and 95%CIs for the associtation between SF and time until CHD outcome.

Results We include 242,084 subjects with SF levels at baseline. Participants were observed for a median of 8.4 years. During follow-up, 1106 incident cases of CHD were identified. Persons with eleveated SF did not have an increased CHD risk at follow-up (adjusted hazard ratio= 0.99; 95%CI 0.94 – 1.05; p = 0.86 in men, and 0.95; 95%CI 0.81 -1.13; p = 0.60 in women).

Conclusions: Our study, by far the largest, showed that high levels of SF do not confer an increased risk of CHD, and questions its role as a risk factor for this disease.

Keywords: Ferritin, Coronary Heart Disease; Incidence

Introduction

Regardless of geographical variations, cardiovascular disease (CVD) is still the leading cause of death and disability worldwide. In Europe, it is responsable for over 4 million deaths/year, of which coronary heart disease (CHD) accounts for almost half of them [1]. The estimated global cost of CVD is US$ 863 billion, and it is estimated to increase by 22%, leading to US$ 1,044 billion in 2030 [2]. In this context, recent research has focused on the identification of non-traditional risk factors, such as iron biomarkers, which could contribute to further reduce the rates of CHD in the next decades. Among the available iron biomarkers, serum ferritin (SF) has gained importance, since it is the most common measurement of body iron status and correlates well with body iron stores [3]. Prospective and retrospective studies aiming to determine the association between SF and CVD [4] or CHD have reported conflicting results [3–6]. Despite several biological mechanisms, such as oxidation of lipids [7] or damage produced by oxygen free radicals, have been proposed to explain how iron stores could increase the risk of CHD [8], the exact pathological pathway is still to be elucidated [9]. To our knowledge, there have been no studies analysing this association in a Mediterranean population. Improving our capacity to assess individual and population risk of these diseases is a constant challenge for public health policy-makers and primary healthcare systems and therefore being able to identify additional cardiovascular risk factors in our population can contribute not only to an early diagnosis, but could also add prognostic information for patients who already have CHD. Given the special features of the Mediterranean diet and its protective role regarding CHD [10], results of previous studies analysing the association between iron status and CHD may not be applicable to our population and, therefore, the aim of this study is to determine the prognosis value of SF in the incidence of CHD using real-world data.

Materials and methods

Study design

Cohort study using a primary health care population database.

Source of data

Data are obtained from SIDIAP database ("*Sistema d'informació per al desenvolupament de la Investigació en Atenció Primària*", www.sidiap.org), CMBD-AH ("*Conjunt mínim bàsic de dades*") and the official death registry of the government.

The SIDIAP database gathers anonymized information on medical records for > 5.8 million patients (which covers >80% of the population of Catalonia). This database nourished itself from the electronic medical records software used by primary care profesionals (ECAP), which contains information on demographic data (date of birth, sex, nationality), acute and chronic health conditions (ICD-10 Code), laboratory tests (taken directly from the laboratories), prescriptions dispensed by pharmacies (through pharmacy invoices) and referrals to the specialists.

Study participants

Subjects aged between 35 and 74 years, for whom serum ferritin measurements at baseline (January 1, 2006 to December 31, 2008) were available, and without any known cardiovascular disease at baseline were included.

Exclusion criteria

All subjects with previous history of cardiovascular disease including CHD (angina, myocardial Infarction, coronary revascularization procedures), stroke (ischemic or hemorrhagic, including transient ischemic attacks), and peripheral artery disease diagnosed with vascular imaging techniques were excluded.

Futher exclusion criteria were: history of illegal drug use and chronic alcoholism (or total daily alcohol intake >50g/day). Participants were also excluded if they had or were diagnosed with hemochromatosis, chronic conditions (such as liver, rheumatic or kidney disease), acute infection or inflammation, as well as those institutionalized, those who used iron supplements or reporting high protein C reactive levels or low levels of hemoglobin (<10 g/dL), VCM (<80) or any other iron

biomarker (to exclude patients with high levels of ferritin secondary to inflammatory disease).

Follow-up:

Participants were observed from 1st January, 2006 until death, moving out of the catchment area or end of follow-up (31st December, 2016).

Outcomes:

Incidence of ischemic heart disease or CHD was defined as acute myocardial infarction (fatal or nonfatal or angina (ICD-10: I21, I210-I219, I22, I220-I240, I241, I248 and I249).

Clinical and biochemical variables

Sociodemographics data: age at baseline, sex. Classical cardiovascular risk factors were defined as hypertension patients with diagnostic codes (ICD10: I10 – I13) or treatment with antihypertensive drugs; dyslipemia (diagnostic code E78.x or treatment with cholesterol-lowering drugs), type 2 diabetes (diagnostic codes E11.x or antidiabetic treatment (oral or insulin); smoking status (former/current/non-smoker), body mass index (BMI). All these diagnoses were recorded at baseline. Drug prescriptions were also assessed (identified from dispensing records): aspirin, and other antiplatelets. Risk of alcoholism was measured with AUDIT test, and categorized from 0 (zero risk) to 3 (high risk). White blood cells couns was used as a meaure of inflammation when available. SF levels were measured by immunotrubidimetry (intra- and interassay coefficients of variation<8).

Statistical analysis

Descriptive analyses of baseline characteristics are presented as mean, standard deviation, 95% confidence intervals, median, and inter-quartile range (for continuous variables) or N (%) for categorical/binary data. Serum ferritin variable was described using z-scores of ferritin values (as continuous variable), and also categorized into quartiles. A set of confounders (age, sex, BMI, smoking and classical cardiovascular risk factors as diabetes, hypertension and dyslipemia) were defined *a priori* and adjusted for to explore either confounding or potential causal pathways. Incidence rates (IR) and 95% CI of the main outcomes were estimated assuming a normal distribution for the cumulative incidence and a Poisson distribution for the incidence density. Cox regression models were used to compute raw and adjusted (age, sex, BMI, smoking, diagnose of hypertension,

diabetes, dyslipidemia, treatment of hypertension, diabetes, dyslipidemia) hazard ratios (HRs) and 95%CIs for the association between SF and time until CHD outcome. Change in risk of CHD per one increase standard deviations (SD) of serum ferritin was calculated. In case of quartiles of ferritin, the first quartile was used as reference. The level of statistical significance used for hypothesis testing was 0.05. Further sensitive analyses were carried out stratifying the results by sex. Analyses were carried out using the program R versión 3.2.5 for Windows.

Ethical considerations

The study was planned and executed in accordance with the principles laid down in the Helsinki declaration (World Medical Association) and the standards of good practice in clinical research. The study protocol was approved by the Ethics Committee at institution.

Results

Baseline characteristics:

A total number of 242,084 subjects with ferritin levels were analysed. The majority were healthy middle-aged women with normal levels of serum iron biomarkers. When analysing the baseline characteristics according to the quartiles of ferritin (Table 1) and comparing to lower levels, subjects with higher levels of ferritin were predominantly older men (mean age of 55 years old and 66% of men), smokers (21.4%) and at risk of alcoholism (36.8%).

Cummulative incicence rate of CHD during the study period:

Participants were observed for a median of 8.4 years (IQR from 7.6 to 9.1). During this period, 1106 incident cases of CHD were identified out of 130,099 subjects analysed, which represented a crude incidence rate of 10 cases per 10,000 persons/year. An increasing incidence of coronary heart was found per each increase of 1SD of ferritin (Fig.1).

Association between serum levels (SF) of ferritin and myocardial infarction (MI) stratified by sex:

Kaplan-Meier analysis stratified by sex and age (under and over 50 years old) are reported in Fig.1. In

Cox regression models, compared with those in the first quartile of ferritin, only women over 50 years in the 2nd, 3rd and 4th quartile of SF reported a borderline statistically significant lower risk of being diagnosed with MI in the crude and adjusted for potential confounders models (HR of 0.74 95%CI 0.54 to 1.01, HR of 0.57, 95% CI 0.42 to 0.79 and HR of 0.71, 95% CI 0.51 to 1.00, respectively). This borderline association disappeared when using continuous levels of ferritin instead of quartiles (Table 2).

Discussion

Key findings

In this cohort study based on a large primary care population database, a total of 242,084 subjects with serum ferritin levels available were followed for a median of 8.4 years (IQR of 7.6 to 9.1). After stratifying by sex, adjusting for potential confounders, and comparing to those with SF in the 1st quartile, women over the age of 50 with SF levels of at least 30 mg/dL reported a borderline statisticaly significant decreased risk of 26 to 46% of being diagnosed with MI, however, this decreased risk lost significance when using continuous ferritin instead of quartiles. No further associations were found for women under 50 years of age or for men.

Comparison with other studies

Since Sullivan suggested the iron hypothesis to explain sex differences in cardiovascular diseases [11], many studies have aimed to confirm these findings with uneven results [4]. Several prospective and retrospective studies have been published supporting this association [12–20], with results ranging from 1.6 to 6.7 fold-increased risk of suffering a CHD among those with higher levels of body iron stores [12,14,15,17–19].Conversely, in our study, we did not find an increased risk of CHD among subjects in the highest quartiles of SF. Some of the limitations of the aforementioned studies included the small sample size analyzed [12–17], the selection of only men [14,17–19] or the cross-sectional designs [12–14]. Conversely, our study was carried out using a population database covering over 5 million men and women in Catalonia, with a large number of MI identified (1106 out of 130,105 subjects) followed up during a long period of time (>8 years), allowing us to easily

extrapolate our results.

The iron biomarker used as a representation of body iron store is also a source of inconsistency through the previous studies; few of them used SF as the iron biomarker analysed [12,14,19,20] and the association was mostly detected in subjects already at high risk of suffering a CHD [12,14,15]. We used SF given the fact that it correlates well with body iron stores [3] and, to account for the possible influence of infection or inflammation, those with high levels of PCR or anemia were excluded. Furthermore, the majority of these studies were carried out in Asian, American or Northern European countries [12,14–19], with different population characteristics and prevalences of CVD [21] which make hard the comparison with our results.

Our results are partially in accordance with other studies [22–25] that did not find an association between SF and the incidence of CHD, either clinical or angiographically diagnosed. Despite finding a statistically significant borderline protective effect of SF levels over 30 for CHD, this association disappeared once analysing ferritin continuously. This migh be due to the fact that quartiles were divided arbitrarily and therefore the analysis using continuous ferritin levels could be a better reflection of reality. As in our study, previous publications also included large sample sizes [22–24] and were followed for similar periods of time [24,25] .

If the association between body iron stores and CHD indeed exists, our negative results could be explained by the overall lower prevalence of CHD in our population compared to other European countries [26] compared to the populations analysed in other studies. Furthermore, the different validity and reliability of the iron biomarkers used across previous studies, including ours, could be the reason of the conflicting results. Finally, another constrain for the comparison our results with the rest of the publications is the difference in outcomes measured (acute myocardial infarction, coronary artery disease, coronary artery calcium or carotid aterosclerosis), which could contribute to the different results found.

Limitations to our study

Despite the strengths of our study, which includes the analysis of a large population database, some limitations need to be considered. First, there are limitations inherent to observational studies carried

out with databases such as retrospective infomation and registration bias. Second, given that SF is known to increase under certain circumstances such as inflammation, adjusting for blood leucocytes or CRP has been used in studies to circumvent the confounding effect of inflammation. In our study, despite excluding those subjects with very high levels of CRP (>20 mg/dl), we had a large number of missing measurements (approximately 60%) and we were not able to analyse blood leucocytes since it is not routinely asked for in primary care, which could have influenced our results. Therefore, we cannot fully rule out the possibility that the high levels of SF reflect the inflammatory state of the subjects rather than an increased risk of CHD. Third, ferritin levels were only accounted for at baseline. Not taking variations into account could result in an over or underestimation of the association. At last, we could not account for the associaton between other iron parameters and CHD and therefore are results are limited to SF levels. Further studies analysing the influence of the other iron biomarkers on CHD are needed.

Generazability of the study

The present epidemiological study was based in a large population database (SIDIAP) which is nourished by routinely based medical information of >5 million subjects in Catalonia. The characteristics of the data included (its representativeness [27] and its routinely based medical information) enables us to extrapolate our results to the rest of the Mediterrenean population. The studies included in the meta-analysis have been conducted in Nordic countries, France, Netherlands, USA or Australia, which allows a generalization of the results.

Conclusion

Overall, contrary to the iron hypothesis, the results of our study suggest that high levels of serum ferritin are not associated with increase risk of CHD in both genders.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

CR wrote the first draft of the manuscript. GFM conceived and designed the study. NAP, CRR, JBG, VAV supervised the analysis, edited the manuscript and contributed to the discussion.

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Table 1. Baseline characteristics of participants according to ferritin quartiles

	Serum ferritin (mg/dl)			
	[0,30.7] n = 60,600	**(30.7,64] n = 60,674**	**(64,132] n= 60,496**	**(132,3.96e+03] n = 60,314**
Age				
Mean (SD)	47.06 (9.86)	51.11 (11.25)	54.75 (11.20)	55.27 (11.16)
Sex				
Females	57,173 (94.34%)	53,066 (87.46%)	41,993 (69.41%)	20,238 (33.55%)
Body Mass Index				
Mean (SD)	26.92 (5.47)	27.35 (5.39)	28.17 (5.21)	28.85 (4.87)
Missing	10,350 (17.08%)	8,665 (14.28%)	7,462 (12.33%)	7,547 (12.51%)
Smoking status				
No smoker	17,916 (29.56%)	20,546 (33.86%)	21,941 (36.27%)	18,997 (31.50%)
Current	10,945 (18.06%)	11,035 (18.19%)	10,688 (17.67%)	12,941 (21.46%)
Former	3,579 (5.91%)	3,692 (6.08%)	4,225 (6.98%)	6,455 (10.70%)
Missing	28,160 (46.47%)	25,401 (41.86%)	23,642 (39.08%)	21,921 (36.34%)
Risk of alcoholism				
0	37,276 (61.51%)	37,711 (62.15%)	36,018 (59.54%)	28,850 (47.83%)
1	10,207 (16.84%)	11,535 (19.01%)	14,232 (23.53%)	19,626 (32.54%)
2	508 (0.84%)	664 (1.09%)	1,044 (1.73%)	2,537 (4.21%)
3	5 (0.01%)	8 (0.01%)	17 (0.03%)	30 (0.05%)
Missing	12,604 (20.80%)	10,756 (17.73%)	9,185 (15.18%)	9,271 (15.37%)
Ferritin				
Mean (SD)	17.87 (7.47)	46.02 (9.63)	93.04 (19.30)	279.43 (212.40)
Iron				
Mean (SD)	70.30 (37.42)	82.06 (34.68)	85.01 (34.12)	94.41 (40.00)
Missing	11,924 (19.68%)	13,555 (22.34%)	14,189 (23.45%)	14,499 (24.04%)
Trasferrin				
Mean (SD)	294.72 (51.66)	267.09 (44.58)	256.30 (41.27)	247.06 (43.12)
Missing	49,800 (82.18%)	51,617 (85.07%)	51,734 (85.52%)	49,438 (81.97%)
Hemoglobin				
Mean (SD)	13.06 (1.24)	13.66 (1.12)	14.08 (1.25)	14.72 (1.40)
Missing	32 (0.05%)	33 (0.05%)	49 (0.08%)	76 (0.13%)
Hematocrit				
Mean (SD)	39.27 (3.52)	40.81 (3.35)	41.97 (3.74)	43.59 (4.20)
HCM				
Mean (SD)	29.03 (2.62)	29.89 (2.10)	30.01 (2.20)	30.44 (2.57)
VCM				
Mean (SD)	87.38 (6.56)	89.38 (5.54)	89.58 (5.93)	90.29 (6.92)
PCR				
Mean (SD)	6.22 (18.72)	6.99 (20.54)	7.89 (21.86)	10.35 (28.00)
Missing	37,209 (61.40%)	36,177 (59.63%)	35,690 (59.00%)	36,706 (60.86%)
Dyslipemia	5,339 (8.81%)	8,702 (14.34%)	11,965 (19.78%)	13,488 (22.36%)
Diabetes	2,529 (4.17%)	3,165 (5.22%)	4,288 (7.09%)	6,297 (10.44%)
Hypertension	9,698 (16.00%)	13,779 (22.71%)	18,167 (30.03%)	19,922 (33.03%)
Cumulative incidence of CHD	213 (0.35%)	280 (0.46%)	441 (0.73%)	754 (1.25%)

1

Table 2. Multivariate adjusted hazards ratio of association per one standard deviation increase of serum ferritin with coronary heart disease.

	Men	**Women (all ages)**	**Women Age > 50 years**
	Hazard Ratio (95%CI; *p* value)	**Hazard Ratio (95%CI; *p* value)**	**Hazard Ratio (95%CI; *p* value)**
Ferritin (z score of ferritin)	0.99 (0.94 – 1.05; $p = 0.86$)	0.95 (0.81 -1.13; $p = 0.60$)	0.99 (0.83 – 1.17; $p = 0.88$)
Age (years)	1.48 (1.34 – 1.64; $p < 0.001$)	2.28 (1.93 – 2.71; $p < 0.001$)	2.47 (1.36 – 4.51; $p = 0.003$)
Body Mass Index	0.99 (0.97 – 1.01; $p = 0.28$)	1.02 (0.99 – 1.03; $p = 0.08$)	1.001 (0.99 – 1.03; $p = 0.41$)
Tab*smoker	1.74 (1.47 – 2.05; $p < 0.001$)	2.96 (2.34 – 3.74; $p < 0.001$)	2.74 (2.10 – 3.58; $p < 0.001$)
Baseline hypertension	1.58 (1.34 – 1.86; $p < 0.001$)	1.55 (1.23 – 1.95; $p < 0.001$)	1.51 (1.18 – 1.94; $p = 0.001$)
Baseline diabetes	1.22 (1.00 – 1.47; $p = 0.05$)	2.25 (1.76 – 2.87; $p < 0.001$)	2.07 (1.60 – 2.69; $p < 0.001$)
Baseline dyslipemia	1.39 (1.06 – 1.83; $p = 0.02$)	1.13 (0.76 – 1.69; $p = 0.53$)	1.16 (0.75 – 1.78; $p = 0.50$)

Figure 1. Coronary heart incidence per 100 participants in relation to ferritin quantiles

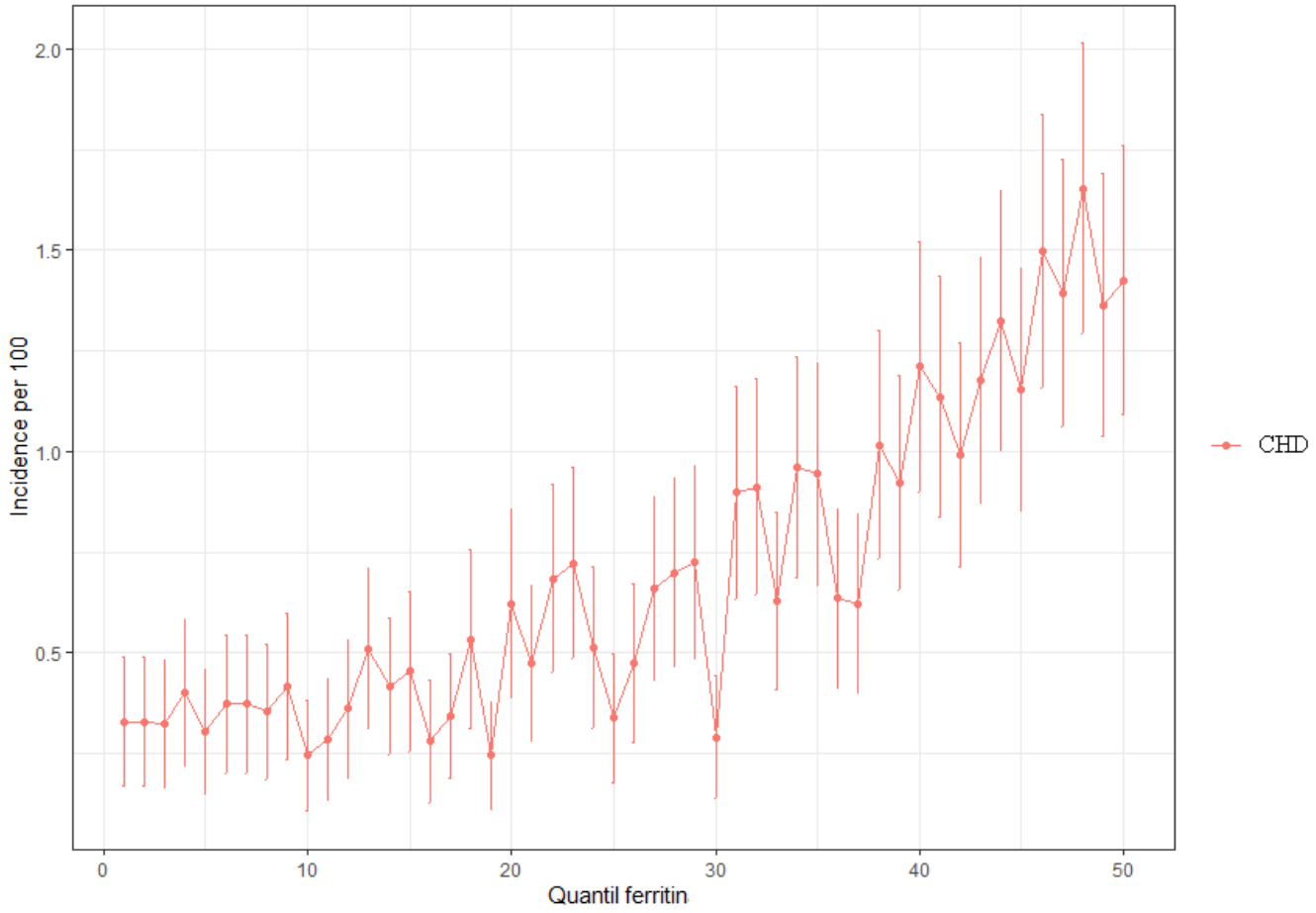
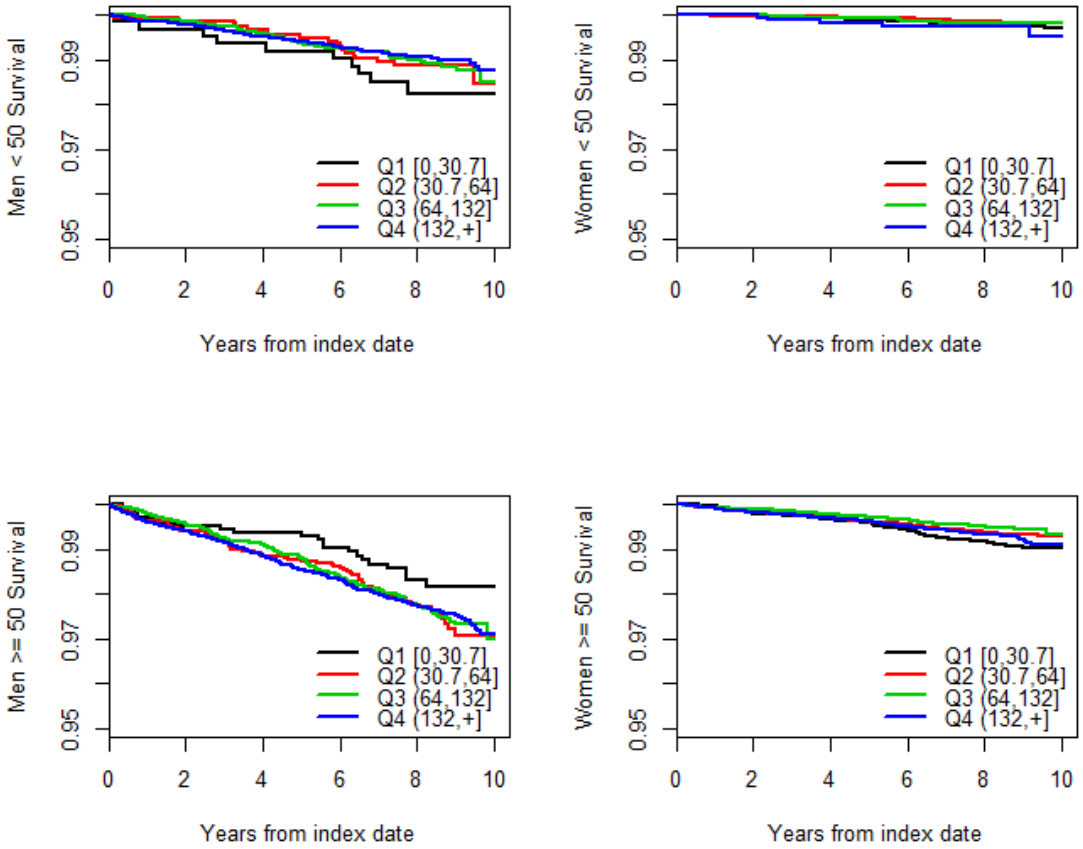


Figure 2. Kaplan-Meier analysis stratified by sex and age (under and over 50 years)



Highlights

High levels of serum ferritin do not confer an increased risk of CHD in a Mediterranean population.

Protective effect of levels of serum ferritin over 30 for CHD disappeared once analyzing ferritin continuously

The analysis using continuous ferritin levels are a better reflection of reality