Plasma Fibrinogen Levels and All-Cause and Cause-specific Mortality in an Italian Adult Population: Results from the Moli-sani Study

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Bleeding, Thrombosis, and Vascular Biology
Vol 2, No 1 (2023)
https://doi.org/10.4081/btvb.2023.46

Appendix S1: Blood Sample collection, storage, shipment and quality check.

Venous blood samples were previously obtained by venipuncture between 07:00 am and 09:00 am from participants who had fasted overnight and had refrained from smoking for at least 6 hours [1]. Citrated plasma samples for this study were initially stored in straws containing the sample code and barcode in liquid nitrogen in a dedicated biobank [2].

They were express-shipped in 3 batches on dry ice to Synapse Research Institute, Maastricht, the Netherlands on 27-10-2016, 08-05-2017 and 23-06-2017, where they were immediately stored at -80°C. Levels of labile coagulation factors (FV, FVIII, and FIX) were determined in a subset of 144 samples from the first batch to confirm plasma sample quality. All coagulation factors measured were within the previously established reference ranges.

Appendix S2: description of the common risk factors assessment and additional references.

Definition of baseline characteristics

During the baseline visit, structured questionnaires to collect personal and clinical information, including socioeconomic status, physical activity, physiopathological medical history, risk factors for CVD and/or tumor, and drug use, and dietary habits were administered.

History of cardiovascular disease (including angina, myocardial infarction, revascularization procedures, cerebrovascular events and peripheral artery disease) and cancer were self-reported by participants during the baseline visit. All medical history reported were confirmed if participant: 1) reported the date of admission to the hospital; b) reported drug use for the specific disease; c) presented medical records of disease diagnosis [3]. We also collected participant reports of physician-made diagnosis of liver disorders.

The dataset of Moli-sani Study provides accurate information on the use (frequency, dose, compliance) of medication for any disease, collected during the recruitment. The questionnaire on drug use was directly linked to the Italian National drug index. Use of antithrombotic (antiplatelet,

heparin or vitamin k antagonists), oral contraceptives, anti-hypertensive, dyslipidaemia and diabetes medications and hormonal therapy were collected and dichotomized as no/yes.

Urban or rural environments were defined on the basis of the urbanization level as described by the European Institute of Statistics (EUROSTAT definition) and obtained by the tool 'Atlante Statistico dei Comuni' provided by the Italian National Institute of Statistics [4]. Educational attainment was based on the highest qualification attained and categorized as low (up to lower secondary school; approximately ≤ 8 years of study) or high (upper secondary education or higher; approximately ≥ 9 years of study). Household income was a three-level variable (< 40,000; ≥ 40,000 Euros/year), with missing values collapsed into a non-respondent category [5]. Physical activity was assessed by a structured questionnaire (24 questions on working time, leisure time, weekly walking and sport participation) and expressed as daily energy expenditure in metabolic equivalent task-hours (MET-hour)[6]. Physical activity was categorized in tertiles [T1-low (range): 19.10-39.66 MET-hour/day; T2-medium: 39.67-42.42 MET-hour/day and T3-high: 42.43-120.25 MET-hour/day] [6]. Subjects were classified as "non-smokers" if they had smoked less than 100 cigarettes in their lifetime, or they had never smoked cigarettes, as "current smokers" those who reported having smoked at least 100 cigarettes in their lifetime and still smoked or had quit smoking within the preceding year, and "former smokers" if they had smoked cigarettes in the past and had stopped smoking for at least one year.

Body mass index (BMI), calculated as kg/m^2 and then grouped into three categories as normal (≤ 25 kg/m^2), overweight (> 25 < 30 kg/m^2) or obese (≥ 30 kg/m^2).

D-dimer levels were measured on fresh citrated plasma by an automated latex-enhanced immunoassay (HemosIL-IL, Milan, Italy). Quality control was maintained using an internal laboratory standard in-house plasma pool. Inter and intra-day variability coefficients were 5.4% and 7.6%, respectively [7].

High sensitivity C-reactive protein (hs-CRP) was measured in fresh serum samples by a particle-enhanced immunoturbidimetric assay (ILab 350, IL, Milan, Italy). Quality control for hs-CRP was

maintained using in-house serum pool and internal laboratory standard; inter-day coefficients of variability for CRP were 5.5% and 4.2%, respectively [5].

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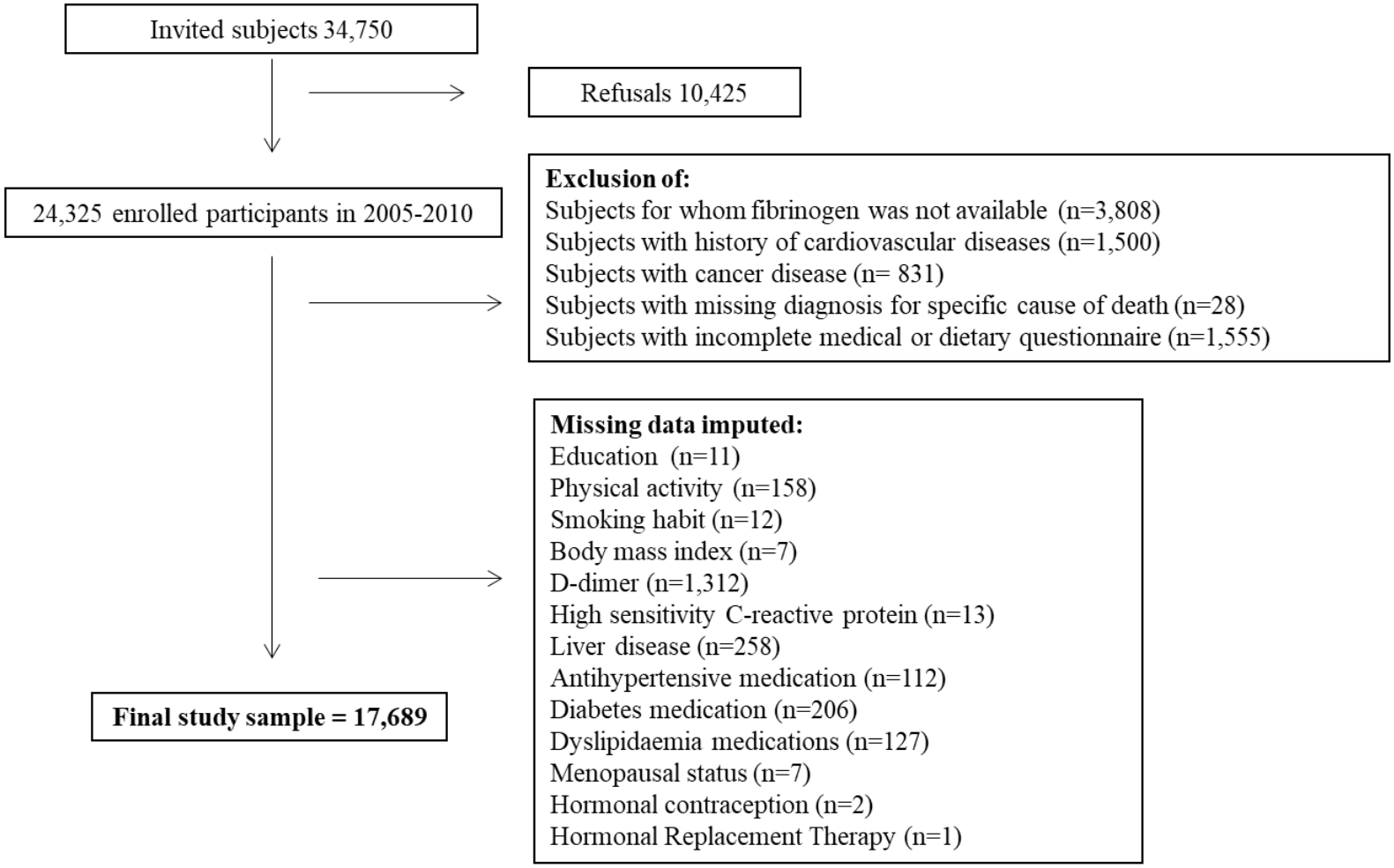
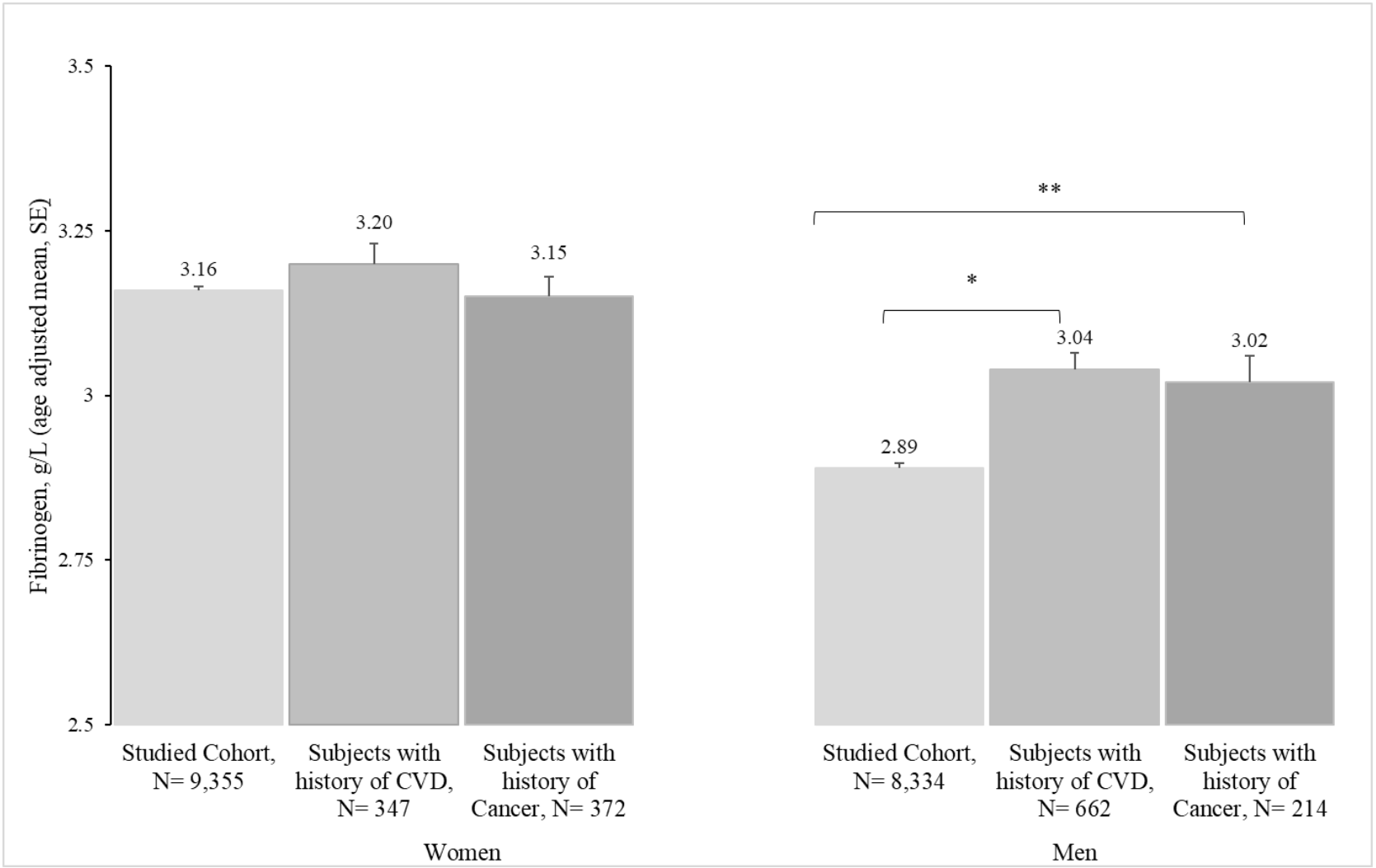
Figure S1. Flow chart of selection of the studied participants from the Moli-sani Cohort.



The groups of eliminated participants (out of the 24,325 recruited at baseline) are overlaid. The final study sample cannot be calculated as a subtraction of the sum of eliminated groups out of the recruited subjects at baseline.

Figure S2. Distribution of fibrinogen levels (means and standard error) in the final study cohort and in excluded individuals according to history of cancer or CVD



*p value < 0.0001; ** p value <0.01.

Table S1. Hazard ratio and 95% CI for all-cause mortality according to baseline risk factors

Characteristics		Women		Men	
N		9,355		8,334	
		HR (95% CI)	**P value***	**HR (95% CI)**	**P value***
Age, years		1.13 (1.12-1.14)	<.0001	1.13 (1.12-1.13)	<.0001
Residence	*Urban vs Rural*	1.01 (0.81-1.24)	0.96	0.85 (0.72-1.00)	0.047
Education	*High school or higher vs Up to lower secondary school*	0.84 (0.66-1.06)	0.14	0.72 (0.60-0.86)	0.002
Income					
	≥ 40000 €/year vs < 40000 €/year	0.79 (0.50-1.26)	0.33	0.72 (0.54-0.96)	0.025
	Not responders vs < 40000 €/year	1.00 (0.82-1.22)	0.99	1.12 (0.94-1.33)	0.20
BMI,kg/m^2					
	Overweight vs Normal weight	0.88 (0.68-1.15)	0.36	1.01 (0.82-1.25)	0.91
	Obese vs Normal weight	1.26 (0.98-1.62)	0.076	1.21 (0.97-1.52)	0.087
Physical Activity					
	Medium vs Low	0.82 (0.66-1.02)	0.074	0.93 (0.77-1.12)	0.43
	High vs Low	0.86 (0.66-1.11)	0.25	0.81 (0.64-1.029	0.072
Smoking habit,					
	Current Smoker vs Never Smoker	1.44 (1.08-1.93)	0.014	2.48 (1.98-3.10)	<.0001
	Former Smoker vs Never Smoker	0.65 (0.44-0.96)	0.032	1.28 (1.06-1.56)	0.013
Alcohol consumption (g/day)		1.00 (0.99-1.01)	0.80	1.00 (1.00-1.00)	0.47
D-dimer (ng/dL) (log)		1.11 (0.96-1.28)	0.16	1.18 (1.06-1.32)	0.0035
hs-CRP (mg/L) (log)		1.18 (1.07-1.30)	0.0011	1.25 (1.15-1.35)	<.0001
Antithrombotic medication		1.94 (1.46-2.57)	<.0001	1.50 (1.17-1.93)	0.0013
Liver disease		1.87 (1.28-2.75)	0.0013	1.32 (0.95-1.82)	0.096
Antihypertension medications		1.27 (1.03-1.56)	0.022	1.00 (0.85-1.17)	0.96
Diabetes medications		2.08 (1.52-2.84)	<.0001	1.60 (1.27-2.01)	<.0001
Hypercholesterolemia medications		0.91 (0.67-1.23)	0.53	0.87 (0.63-1.21)	0.41
ONLY IN WOMEN					
Hormonal contraception		0.94 (0.64-1.37)	0.74		
Menopausal status		0.51 (0.33-0.78)	0.0021		
Hormonal Replacement Therapy		0.68 (0.41-1.12)	0.13		

Abbreviation: CI: confidence interval and HR: Hazard ratio. ***P value** age adjusted

Figure S3. Distribution of plasma fibrinogen in women (N= 9,355) and men (N= 8,334) of the Moli-sani cohort

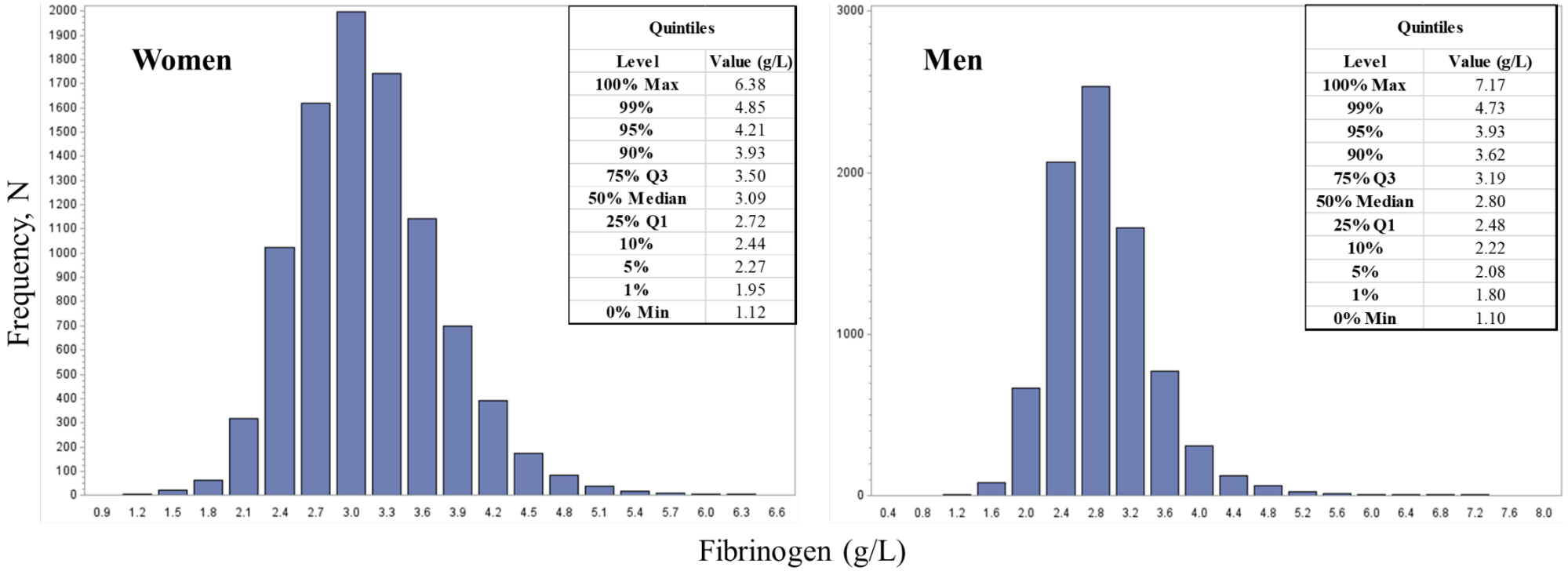


Table S2. Hazard Ratios (95% confidence interval) for all-cause and cause-specific mortality according to plasma fibrinogen quintiles, stratified by sex and in case complete analyses (women N= 8,944, men N= 8,006)

	Women Quintiles of Fibrinogen						Men Quintiles of Fibrinogen					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P value**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**P value**
Fibrinogen range, g/L	1.12-2.64	2.65-2.96	2.97-3.23	3.24-3.61	3.62-6.38		1.10-2.41	2.42-2.68	2.69-2.94	2.95-3.30	3.31-7.17	
					All-cause mortality							
N events/ N total	46/1,787	43/1,791	54/1,790	96/1,787	152/1,789		56/1,605	89/1,598	99/1,601	134/1,601	215/1,601	
Death rate (95% CI) /10,000 Person Years	23.0 (17.2-30.6)	21.2 (15.7-28.6)	26.7 (20.5-34.9)	47.7 (39.1-58.3)	77.4 (66.1-90.8)		31.2 (24.0-40.5)	49.9 (40.5-61.4)	55.9 (45.9-68.1)	76.3 (64.4-90.3)	124.8 (109.2-142.7)	
HR Crude (95% CI)	0.87 (0.58-1.28)	0.79 (0.53-1.18)	Ref.	1.79 (1.28-2.49)	2.95 (2.16-4.02)	<.0001	0.55 (0.40-0.77)	0.89 (0.67-1.18)	Ref.	1.37 (1.05-1.77)	2.25 (1.77-2.85)	<.0001
HR_1 (95% CI)	1.91 (1.28-2.83)	1.05 (0.70-1.57)	Ref.	1.34 (0.96-1.88)	1.76 (1.29-2.40)	0.0002	0.85 (0.61-1.19)	1.12 (0.84-1.49)	Ref.	1.15 (0.89-1.50)	1.45 (1.14-1.84)	0.0018
HR_2 (95% CI)	1.91 (1.28-2.84)	1.06 (0.71-1.58)	Ref.	1.31 (0.94-1.84)	1.63 (1.19-2.23)	0.0016	0.89 (0.64-1.24)	1.19 (0.89-1.59)	Ref.	1.16 (0.89-1.50)	1.39 (1.09-1.77)	0.015
					Cardiovascular mortality							
N events/ N total	13/1,787	14/1,791	18/1,790	39/1,787	65/1,789		12/1,605	25/1,598	27/1,601	49/1,601	76/1,601	
Death rate (95% CI) /10,000 Person Years	6.5 (3.8-11.2)	6.9 (4.1-11.6)	8.9 (5.6-14.1)	19.4 (14.2-26.5)	33.1 (26.0-42.2)		6.7 (3.8-11.2)	14.0 (9.5-20.7)	15.2 (10.5-22.2)	27.9 (21.1-36.9)	44.1 (35.2-55.2)	
HR Crude (95% CI)	0.74 (0.36-1.50)	0.78 (0.39-1.56)	Ref.	2.18 (1.24-3.80)	3.79 (2.25-6.39)	<.0001	0.44 (0.22-0.86)	0.91 (0.53-1.57)	Ref.	1.83 (1.14-2.93)	2.92 (1.88-4.52)	<.0001
HR_1 (95% CI)	1.98 (0.97-4.04)	1.07 (0.53-2.15)	Ref.	1.49 (0.85-2.60)	1.99 (1.18-3.36)	0.040	0.72 (0.36-1.42)	1.19 (0.69-2.05)	Ref.	1.48 (0.93-2.38)	1.75 (1.13-2.72)	0.014
HR_2 (95% CI)	2.20 (1.07-4.53)	1.13 (0.56-2.28)	Ref.	1.45 (0.83-2.55)	1.77 (1.04-3.00)	0.11	0.74 (0.38-1.48)	1.27 (0.74-2.20)	Ref.	1.54 (0.96-2.46)	1.69 (1.09-2.63)	0.029
					Cancer mortality							
N events/ N total	17/1,787	19/1,791	19/1,790	33/1,787	46/1,789		21/1,605	42/1,598	43/1,601	50/1,601	74/1,601	
Death rate (95% CI) /10,000 Person Years	8.5 (5.3-13.6)	9.4 (6.0-14.7)	9.4 (6.0-14.7)	16.4 (11.7-23.1)	23.4 (17.6-31.3)		11.7 (7.6-17.9)	23.5 (17.4-31.9)	24.3 (18.0-32.7)	28.5 (21.6-37.5)	43.0 (34.2-54.0)	
HR Crude (95% CI)	0.91 (0.47-1.75)	1.00 (0.53-1.88)	Ref.	1.74 (0.99-3.07)	2.53 (1.48-4.32)	<.0001	0.48 (0.28-0.81)	0.97 (0.63-1.48)	Ref.	1.17 (0.78-1.76)	1.78 (1.22-2.59)	<.0001
HR_1 (95% CI)	1.42 (0.73-2.75)	1.18 (0.62-2.23)	Ref.	1.49 (0.84-2.62)	1.84 (1.08-3.16)	0.21	0.68 (0.40-1.15)	1.17 (0.77-1.79)	Ref.	1.03 (0.69-1.55)	1.24 (0.85-1.81)	0.17
HR_2 (95% CI)	1.51 (0.78-2.94)	1.21 (0.64-2.29)	Ref.	1.45 (0.82-2.55)	1.63 (0.94-2.81)	0.47	0.74 (0.44-1.26)	1.28 (0.84-1.96)	Ref.	1.03 (0.68-1.54)	1.14 (0.78-1.66)	0.32
					Other-cause mortality							
N events/ N total	16/1,787	10/1,791	17/1,790	24/1,787	41/1,789		23/1,605	22/1,598	29/1,601	35/1,601	65/1,601	

Death rate (95% CI) /10,000 Person Years	8.0 (4.9-13.0)	4.9 (2.7-9.2)	8.4 (5.2-13.5)	11.9 (8.0-17.8)	20.9 (15.4-28.4)		12.8 (8.5-19.3)	12.3 (8.1-18.7)	16.4 (11.4-23.6)	19.9 (14.3-27.7)	37.7 (30.0-48.1)	
HR Crude (95% CI)	0.96 (0.48-1.89)	0.59 (0.27-1.28)	Ref.	1.42 (0.76-2.65)	2.52 (1.43-4.44)	<.0001	0.78 (0.45-1.35)	0.75 (0.43-1.31)	Ref.	1.22 (0.75-1.99)	2.32 (1.50-3.59)	<.0001
HR_1 (95% CI)	2.34 (1.18-4.66)	0.79 (0.36-1.73)	Ref.	1.01 (0.54-1.89)	1.40 (0.79-2.47)	0.030	1.23 (0.71-2.13)	0.95 (0.55-1.66)	Ref.	1.01 (0.62-1.66)	1.45 (0.93-2.25)	0.26
HR_2 (95% CI)	2.15 (1.07-4.32)	0.77 (0.35-1.68)	Ref.	0.99 (0.53-1.85)	1.39 (0.78-2.46)	0.052	1.22 (0.70-2.13)	0.97 (0.55-1.68)	Ref.	0.99 (0.61-1.63)	1.46 (0.94-2.27)	0.24

Model 1: adjusted for age; **Model 2 women:** model 1 plus BMI, education, income, menopausal status, antihypertensive and diabetes medications; **Model 2 men:** model 1 plus BMI, education, smoking habit, physical activity, and diabetes medications. **Abbreviations**: BMI: body mass index; CI: confidence interval and HR: Hazard ratio.

Table S3. Hazard Ratios (95% confidence interval) for all-cause and cause-specific mortality according to plasma fibrinogen quintiles, stratified by sex and excluding early deaths (follow up time ≥ 2 years; women N= 9,329 men N=8,281)

	Women Quintiles of Fibrinogen						Men Quintiles of Fibrinogen					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P value**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**P value**
Fibrinogen Range, g/L	1.12-2.64	2.65-2.96	2.97-3.23	3.24-3.61	3.62-6.38		1.10-2.41	2.42-2.68	2.69-2.94	2.95-3.30	3.31-7.17	
					All-cause mortality							
N events/ N total	46/1,868	42/1,859	53/1,869	96/1,869	156/1,864		57/1,660	92/1,655	98/1,654	131/1,658	208/1,654	
Death rate (95% CI)	21.9	19.9	25.1	45.5	76.0		30.6	49.8	53.4	71.6	115.6	
/10,000 Person Years	(16.4-29.3)	(14.7-26.9)	(19.2-32.8)	(37.2-55.5)	(65.0-88.9)		(23.6-39.7)	(40.6-61.1)	(43.8-65.1)	(60.4-85.0)	(100.9-132.4)	
HR2	1.94	1.10	Ref.	1.30	1.69	0.0009	0.91	1.24	Ref.	1.11	1.30	0.086
(95% CI)	(1.29-2.92)	(0.73-1.65)		(0.92-1.83)	(1.23-2.33)		(0.65-1.28)	(0.92-1.65)		(0.85-1.45)	(1.02-1.66)	
					Cardiovascular mortality							
N events/ N total	11/1,868	13/1,859	16/1,869	42/1,869	66/1,864		12/1,660	27/1,655	27/1,654	49/1,658	73/1,654	
Death rate (95% CI)	5.3	6.2	7.6	19.9	32.2		6.5	14.6	14.7	26.8	40.6	
/10,000 Person Years	(2.9-9.5)	(3.6-10.6)	(4.6-12.4)	(14.7-26.9)	(25.3-40.9)		(3.7-11.4)	(10.0-21.3)	(10.1-21.4)	(20.3-35.5)	(32.3-51.0)	
HR2	2.12	1.22	Ref.	1.61	1.92	0.13	0.73	1.39	Ref.	1.48	1.64	0.058
(95% CI)	(0.98-4.61)	(0.59-2.55)		(0.89-2.90)	(1.10-3.35)		(0.36-1.50)	(0.80-2.43)		(0.91-2.43)	(1.04-2.60)	
					Cancer mortality							
N events/ N total	18/1,868	19/1,859	19/1,869	31/1,869	46/1,864		22/1,660	44/1,655	43/1,654	49/1,658	69/1,654	
Death rate (95% CI)	8.6	9.00	9.0	14.7	22.4		11.8	23.8	23.4	26.8	38.4	
/10,000 Person Years	(5.4-13.6)	(5.7-14.1)	(5.7-14.1)	(10.3-20.9)	(16.8-29.9)		(7.8-18.0)	(17.7-32.0)	(17.4-31.6)	(20.3-35.5)	(30.3-48.6)	
HR2	1.48	1.21	Ref.	1.28	1.68	0.39	0.79	1.29	Ref.	0.95	1.01	0.40
(95% CI)	(0.76-2.88)	(0.64-2.30)		(0.72-2.90)	(0.97-2.90)		(0.47-1.32)	(0.84-1.98)		(0.63-1.44)	(0.68-1.48)	
					Other-cause mortality							
N events/ N total	17/1,868	10/1,859	18/1,869	23/1,869	44/1,864		23/1,660	21/1,655	28/1,654	33/1,658	66/1,654	
Death rate (95% CI)	8.1	4.7	8.5	10.9	21.4		12.4	11.4	15.3	18.0	36.7	
/10,000 Person Years	(5.0-13.1)	(2.6-8.8)	(5.4-13.5)	(7.2-16.4)	(16.0-28.8)		(8.2-18.6)	(7.4-17.4)	(10.5-22.1)	(12.8-25.4)	(28.8-46.7)	
HR2	2.38	0.80	Ref.	0.97	1.41	0.021	1.24	1.00	Ref.	0.99	1.42	0.35
(95% CI)	(1.20-4.72)	(0.36-1.74)		(0.52-1.82)	(0.80-2.51)		(0.70-2.19)	(0.56-1.77)		(0.59-1.64)	(0.90-2.25)	

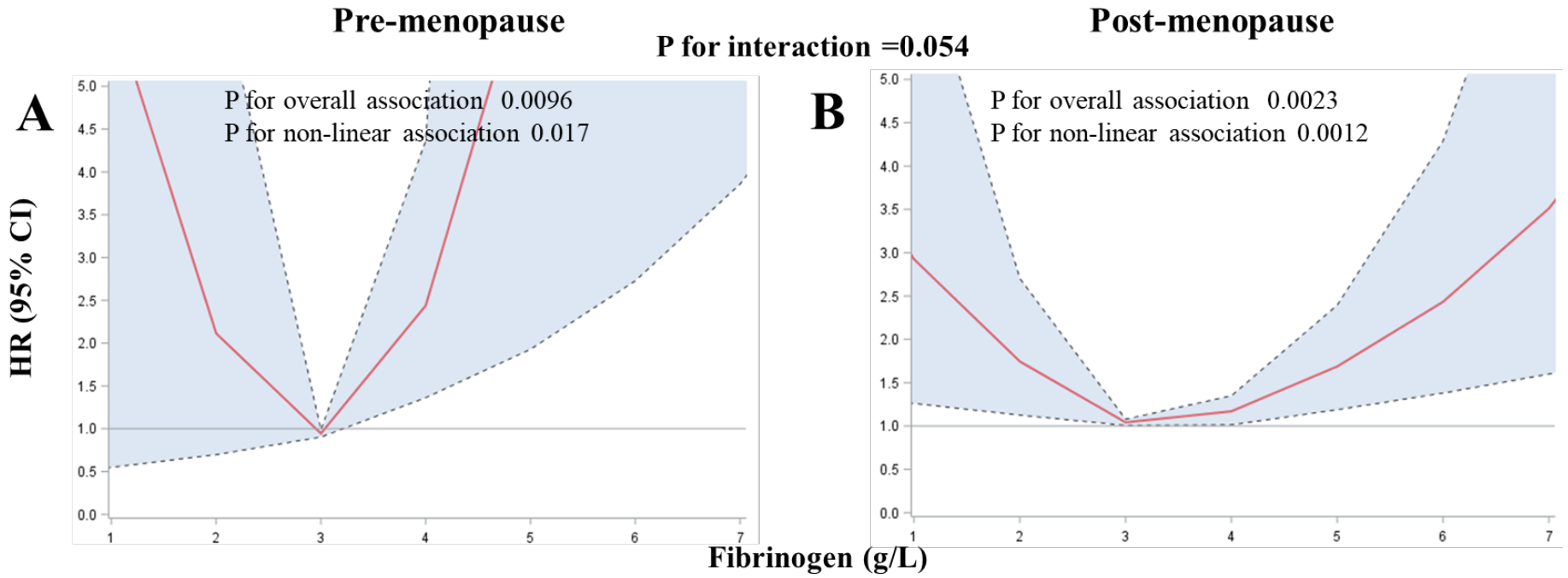
Model 1: adjusted for age; **Model 2 women:** model 1 plus BMI, education, income, menopausal status, antihypertensive and diabetes medications; **Model 2 men:** model 1 plus BMI, education, smoking habit, physical activity, and diabetes medications.
Abbreviations: BMI: body mass index; CI: confidence interval and HR: Hazard ratio.

Table S4. Hazard Ratios (95% confidence interval) for all-cause mortality according to plasma fibrinogen quintiles, stratified by menopausal status in Moli-sani women (N = 9,355)

	Quintiles of Fibrinogen					P value for heterogeneity
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	
Fibrinogen Range, g/L	1.12-2.64	2.65-2.96	2.97-3.23	3.24-3.61	3.62-6.38	
			Pre-Menopause			
N events/ N total	8/1,293	8/1,040	5/836	9/649	10/458	
Death rate (95% CI)	5.5	6.7	5.2	12.1	19.4	
/10,000 Person Years	(2.7-10.9)	(3.4-13.4)	(2.2-12.6)	(6.3-23.3)	(10.4-36.1)	
HR	1.61	0.49	ref	1.53	2.22	0.16
(95% CI)	(0.58-4.49)	(0.13-1.90)		(0.58-4.05)	(0.86-5.73)	
			Post-Menopause			
N events/ N total	40/575	37/829	52/1,035	96/1,221	153/1,412	
Death rate (95% CI)	63.6	39.9	45.0	70.6	99.6	
/10,000 Person Years	(46.6-86.7)	(28.9-55.1)	(34.3-59.0)	(57.8-86.2)	(85.0-116.7)	
HR	2.15	1.09	ref	0.95	1.40	0.0004
(95% CI)	(1.36-3.41)	(0.63-1.63)		(0.67-1.35)	(1.03-1.92)	

Model: adjusted for age, body mass index, education, income, antihypertensive and diabetes medications.
Abbreviations: CI: confidence interval and HR: Hazard ratio.

Figure S4. Dose response curve for all-cause mortality according to plasma fibrinogen levels stratified by menopausal status (panel A: pre-menopause, panel B: post-menopause) in Moli-sani women (N= 9,355)



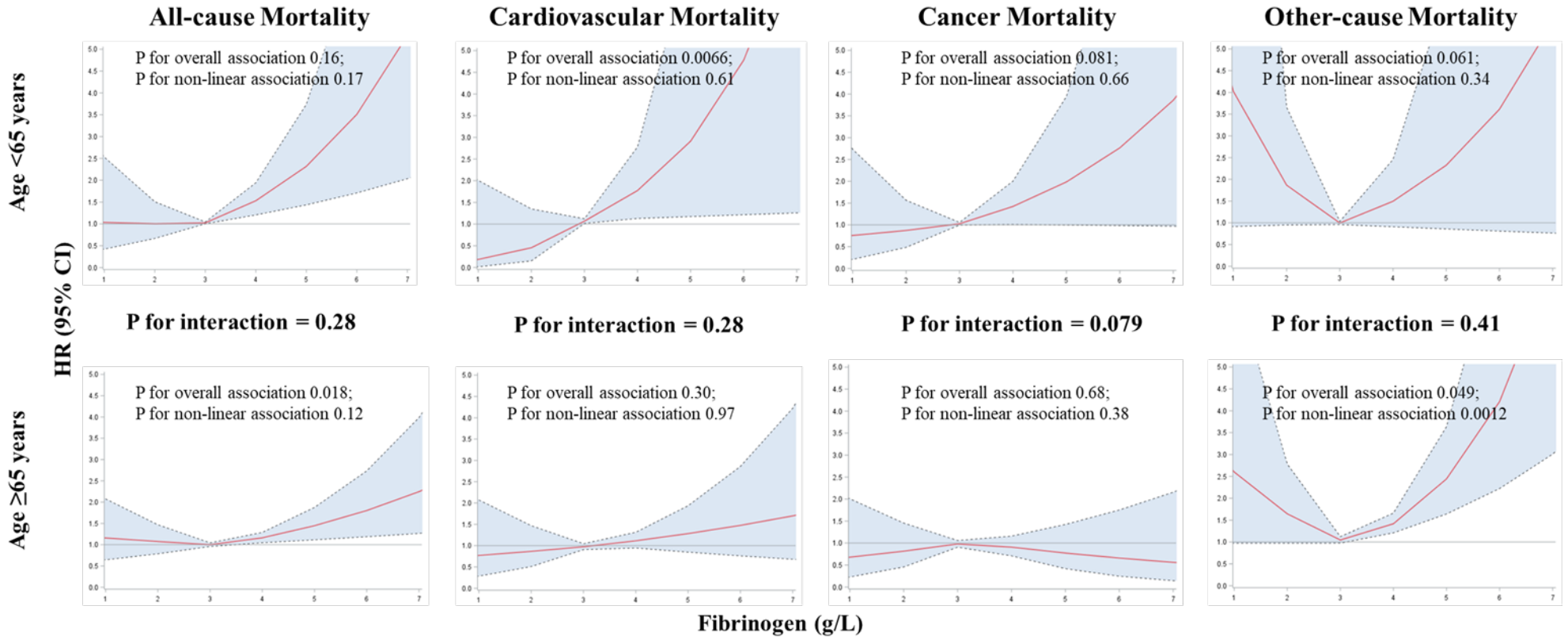
The dose-response curves were obtained from multivariable model adjusted for age, body mass index, education, income, antihypertensive and diabetes medications, by using the first imputed dataset. The other imputed datasets are similar and thus omitted. The reference value of the dose response association is the median value of fibrinogen distribution in women (median 3.09 g/L).
Abbreviations: CI: confidence interval and HR: Hazard ratio.

Table S5. Most frequent other-causes mortality in women (N= 9,355) and men (N= 8,334) of the Moli-sani cohort.

ICD-9* Diagnosis code	System involved or type of disease	Frequency (%)	
		Women	**Men**
460-519	Respiratory	26.5	25.8
520-579	Gastro-intestinal	14.5	17.4
800-999	Injury and poisoning	12.8	16.9
320-359	Nervous	12.0	8.4
240-279	Endocrine, nutritional, metabolic and immunity	6.8	7.9

*ICD-9 International Classification of Diseases 9th revision.

Figure S5. Dose-response curve for all-cause and cause specific mortality according to plasma fibrinogen levels stratified by age classes (<65 years and ≥65 years) in the Moli-sani cohort (N= 17,689)



The dose-response curves were obtained from multivariable model adjusted for sex, age, body mass index, smoking habit, income, physical activity, liver disease, antihypertensive and diabetes medications, by using the first imputed dataset. The other imputed datasets are similar and thus omitted. The reference value of the dose response association is the median value of fibrinogen distribution (median 2.96 g/L).
Abbreviations: CI: confidence interval and HR: Hazard ratio.

Table S6. Assessment of the potential effect of inflammatory and hemostasis biomarkers on the studied outcomes; HR (95%) according to plasma fibrinogen quintiles, stratified by sex in the Moli-sani cohort (women N= 9,355, men N= 8,334)

	Women Quintiles of fibrinogen						Men Quintiles of fibrinogen					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P value**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**P value**
Fibrinogen Range, g/L	1.12-2.64	2.65-2.96	2.97-3.23	3.24-3.61	3.62-6.38		1.10-2.41	2.42-2.68	2.69-2.94	2.95-3.30	3.31-7.17	
					All-cause mortality							
HR (95% CI)	1.98 (1.30-3.01)	0.90 (0.57-1.41)	Ref.	1.00 (0.72-1.39)	1.45 (1.08-1.96)	0.0001	0.94 (0.71-1.24)	1.07 (0.83-1.38)	Ref.	1.24 (0.97-1.58)	1.31 (1.03-1.67)	0.052
HR (95% CI) + hs CRP	2.04 (1.34-3.11)	0.91 (0.58-1.44)	Ref.	0.98 (0.71-1.37)	1.37 (1.01-1.87)	0.0003	1.01 (0.76-1.34)	1.11 (0.86-1.44)	Ref.	1.18 (0.92-1.52)	1.14 (0.89-1.48)	0.66
HR (95% CI) + D.dimer*	1.98 (1.31-3.02)	0.90 (0.57-1.41)	Ref.	1.00 (0.72-1.39)	1.44 (1.07-1.95)	0.0002	0.96 (0.73-1.27)	1.09 (0.84-1.41)	Ref.	1.25 (0.98-1.60)	1.29 (1.02-1.65)	0.16
HR (95% CI) + hs CRP + D.dimer*	2.04 (1.34-3.11)	0.91 (0.58-1.43)	Ref.	0.98 (0.71-1.37)	1.37 (1.01-1.86)	0.0003	1.02 (0.77-1.36)	1.13 (0.87-1.46)	Ref.	1.20 (0.94-1.54)	1.14 (0.88-1.48)	0.63
					Cardiovascular mortality							
HR (95% CI)	1.87 (0.80-4.36)	1.68 (0.81-3.46)	Ref.	1.10 (0.61-1.98)	1.80 (1.06-3.04)	0.056	0.74 (0.43-1.26)	1.03 (0.65-1.62)	Ref.	1.28 (0.83-1.96)	1.33 (0.88-2.02)	0.14
HR (95% CI) + hs CRP	1.88 (0.81-4.41)	1.69 (0.82-3.49)	Ref.	1.09 (0.61-1.97)	1.76 (1.03-3.01)	0.070	0.77 (0.45-1.31)	1.05 (0.66-1.66)	Ref.	1.25 (0.81-1.92)	1.23 (0.79-1.93)	0.41
HR (95% CI) + D.dimer*	1.88 (0.80-4.38)	1.68 (0.82-3.47)	Ref.	1.10 (0.61-1.98)	1.79 (1.06-3.03)	0.063	0.76 (0.45-1.30)	1.05 (0.66-1.66)	Ref.	1.31 (0.85-2.01)	1.32 (0.87-2.00)	0.17
HR (95% CI) + hs CRP + D.dimer*	1.89 (0.81-4.42)	1.69 (0.82- 3.49)	Ref.	1.10 (0.61-1.98)	1.76 (1.03-3.01)	0.081	0.78 (0.46-1.34)	1.07 (0.67-1.69)	Ref.	1.28 (0.83-1.97)	1.24 (0.79-1.93)	0.40
					Cancer mortality							
HR (95% CI)	1.57 (0.83-2.97)	0.38 (0.16-0.93)	Ref.	1.03 (0.62-1.72)	1.17 (0.72-1.90)	0.053	0.69 (0.44-1.08)	1.00 (0.68-1.46)	Ref.	0.97 (0.66-1.43)	0.96 (0.65-1.41)	0.48
HR (95% CI) + hs CRP	1.57 (0.83-2.99)	0.38 (0.16-0.93)	Ref.	1.03 (0.61-1.72)	1.17 (0.71-1.92)	0.053	0.78 (0.50-1.22)	1.06 (0.72-1.56)	Ref.	0.91 (0.62-1.35)	0.78 (0.52-1.178)	0.48
HR (95% CI) + D.dimer*	1.57 (0.83-2.97)	0.38 (0.16-0.93)	Ref.	1.03 (0.62-1.72)	1.18 (0.73-1.91)	0.052	0.70 (0.45-1.10)	1.01 (0.69-1.48)	Ref.	0.98 (0.67-1.45)	0.95 (0.65-1.39)	0.53
HR (95% CI) + hs CRP + D.dimer*	1.58 (0.83-3.00)	0.38 (0.16-0.93)	Ref.	1.03 (0.62- 1.72)	1.17 (0.71-1.94)	0.053	0.79 (0.50-1.24)	1.07 (0.73-1.57)	Ref.	0.92 (0.62-1.36)	0.78 (0.52- 1.17)	0.48
					Other-cause mortality							
HR (95% CI)	2.60 (1.24-5.48)	1.07 (0.47-2.43)	Ref.	0.88 (0.46-1.66)	1.43 (0.81-2.51)	0.022	1.74 (1.04-2.91)	1.28 (0.75-2.18)	Ref.	1.73 (1.05-2.85)	2.00 (1.23-3.25)	0.042

HR (95% CI) + hs CRP	2.84 (1.34-6.00)	1.13 (0.50-2.57)	Ref.	0.84 (0.44-1.60)	1.20 (0.67-2.16)	0.016	1.84 (1.10-3.10)	1.32 (0.77-2.24)	Ref.	1.66 (1.01-2.75)	1.79 (1.08-2.98)	0.10
HR (95% CI) + D.dimer*	2.69 (1.27-5.69)	1.08 (0.48-2.46)	Ref.	0.90 (0.48-1.71)	1.42 (0.81-2.50)	0.045	1.77 (1.06-2.97)	1.30 (0.76-2.20)	Ref.	1.75 (1.06-2.88)	1.98 (1.22-3.22)	0.044
HR (95% CI) + hs CRP + D.dimer*	2.89 (1.36-6.12)	1.13 (0.50-2.56)	Ref.	0.87 (0.46-1.64)	1.21 (0.67-2.17)	0.033	1.86 (1.11-3.13)	1.33 (0.78-2.26)	Ref.	1.68 (1.02-2.79)	1.79 (1.07-2.98)	0.10

***D-dimer** missing by design for N= 1,312 subjects. **Model 1:** adjusted for age; **Model 2 women:** model 1 plus BMI, education, income, menopausal status, antihypertensive and diabetes medications; **Model 2 men:** model 1 plus BMI, education, smoking habit, physical activity, and diabetes medications. **Abbreviations**: BMI: body mass index; CI: confidence interval and HR: Hazard ratio.

Appendix S3: Moli-sani Study Investigators

The enrolment phase of the Moli-sani Study was conducted at the Research Laboratories of the Catholic University in Campobasso (Italy), the follow up of the Moli-sani cohort is being conducted at the Department of Epidemiology and Prevention of the IRCCS Neuromed, Pozzilli, Italy.

Steering Committee: Licia Iacoviello*°(Chairperson), Giovanni de Gaetano* and Maria Benedetta Donati*.

Scientific Secretariat: Marialaura Bonaccio*, Americo Bonanni*, Chiara Cerletti*, Simona Costanzo*, Amalia De Curtis*, Augusto Di Castelnuovo§, Alessandro Gialluisi*°, Francesco Gianfagna°§, Mariarosaria Persichillo*, Teresa Di Prospero* (Secretary).

Safety and Ethical Committee: Jos Vermylen (Catholic University, Leuven, Belgio) (Chairperson), Renzo Pegoraro (Pontificia Accademia per la Vita, Roma, Italy), Antonio Spagnolo (Catholic University, Roma, Italy).

External Event Adjudicating Committee: Deodato Assanelli (Brescia, Italy), Livia Rago (Campobasso, Italy).

Baseline and Follow-up Data Management: Simona Costanzo* (Coordinator), Marco Olivieri (Campobasso, Italy), Teresa Panzera*.

Data Analysis: Augusto Di Castelnuovo§ (Coordinator), Marialaura Bonaccio*, Simona Costanzo*, Simona Esposito*, Alessandro Gialluisi*°, Francesco Gianfagna°§, Sabatino Orlandi*, Emilia Ruggiero*, Alfonsina Tirozzi*.

Biobank, Molecular and Genetic Laboratory: Amalia De Curtis* (Coordinator), Sara Magnacca§, Fabrizia Noro*, Alfonsina Tirozzi*.

Recruitment Staff: Mariarosaria Persichillo* (Coordinator), Francesca Bracone*, Teresa Panzera*.

Communication and Press Office: Americo Bonanni*.

Regional Institutions: Direzione Generale per la Salute - Regione Molise; Azienda Sanitaria Regionale del Molise (ASReM, Italy); Agenzia Regionale per la Protezione Ambientale del Molise (ARPA Molise, Italy); Molise Dati Spa (Campobasso, Italy); Offices of vital statistics of the Molise region.

Hospitals: Presidi Ospedalieri ASReM: Ospedale A. Cardarelli – Campobasso, Ospedale F. Veneziale – Isernia, Ospedale San Timoteo - Termoli (CB), Ospedale Ss. Rosario - Venafro (IS), Ospedale Vietri – Larino (CB), Ospedale San Francesco Caracciolo - Agnone (IS); Casa di Cura Villa Maria - Campobasso; Ospedale Gemelli Molise - Campobasso; IRCCS Neuromed - Pozzilli (IS).

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Moli-sani Study Past Investigators are available at https://www.moli-sani.org/?pageid=173