

Supplementary Materials

Joint association of low muscle mass and mild anemia with all-cause, cardiovascular and cancer mortality among US middle and older adults

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The file includes:

Supplementary Methods

Table S1-S6

Figure S1

Supplementary Methods

Potential Covariates

Smoking statuses were categorized as follows: “never” for individuals who had smoked less than 100 cigarettes in life, “former” for those who had smoked over 100 cigarettes in life but currently do not smoke at all, and “now” for those who had smoked more than 100 cigarettes in life and smoke some days or every day. Alcohol assumption was classified as “never” for individuals who had less than 12 drinks in lifetime, “former” for those who had over 12 drinks in 1 year and did not drink last year or did not drink last year but drank more than 12 drinks in lifetime, and “now” for those had drank every day. Hypertension was identified by a blood pressure of $\geq 140/90$ mmHg, or self-reported diagnoses, or the use of antihypertensive medications. Diabetes mellitus was included an expanded set of diagnostic criteria comprising six reference definitions: the use of antidiabetic medication, fasting glucose level ≥ 7.0 mmol/L, random blood glucose level ≥ 11.1 mmol/L, 2-hour blood glucose level ≥ 11.1 mmol/L during oral glucose tolerance test, glycohemoglobin (HbA1c) $\geq 6.5\%$, and a self-reported the history of diagnose. Hyperlipidemia was quantified by serum lipid levels (triglyceride ≥ 150 mg/dL or total cholesterol ≥ 200 mg/dL or low-density lipoprotein ≥ 130 mg/dL or high-density lipoprotein < 40 mg/dL for males, < 50 mg/dL for females) or the use of lipid-lowering medication. CKD was diagnosed if an individuals presented lower eGFR (< 90 ml/min/1.73 m²) or albuminuria (≥ 30 mg/g). ASCVD was determined as “yes” or “no” by self-reported history of cardiovascular disease (coronary heart disease, angina, heart attack and stroke).

Supplementary tables

Table S1. Addictive and multiplicative of interaction test for the relationship of LMM and MA with all-cause, cardiovascular, and cancer mortality.

Table S2. Independent and joint association of LMM and MA status with all-cause, cardiovascular, and cancer mortality stratified by age

Table S3. Independent and joint association of LMM and MA status with all-cause, cardiovascular, and cancer mortality stratified by gender

Table S4. Joint association of LMM and MA with all-cause, cardiovascular, and cancer mortality among US middle-aged and older adults, NHANES (excluding died within 2 years of follow-up)

Table S5. Association of low muscle mass and mild anemia with cardiovascular and cancer mortality in cause-specific Cox regression models, NHANES 1999–2006 and 2011–2018

Table S6. Fine–Gray competing risk regression of low muscle mass and mild anemia with mortality, NHANES 1999–2006 and 2011–2018

Table S1. Addictive and multiplicative of interaction test for the relationship of LMM and MA with all-cause, cardiovascular, and cancer mortality.

Exposure		HR (95% CI)	P value
All-cause mortality			
LMM	MA		
No	No	Ref.	
No	Yes	1.49 (1.19,1.87)	<0.001
Yes	No	1.40 (1.22,1.60)	<0.0001
Yes	Yes	2.43 (1.82,3.26)	<0.0001
RERI		0.54	
ROR		1.16	
Cardiovascular mortality			
LMM	MA		
No	No	Ref.	
No	Yes	1.37 (0.92,2.04)	0.12
Yes	No	1.39 (1.07,1.79)	0.01
Yes	Yes	3.57 (2.31,5.52)	<0.0001
RERI		1.81	
ROR		1.87	
Cancer mortality			
LMM	MA		
No	No	Ref.	
No	Yes	1.53 (1.01,2.33)	0.05
Yes	No	1.63 (1.23,2.16)	<0.001
Yes	Yes	3.86 (2.22,6.71)	<0.0001
RERI		1.70	
ROR		1.55	

Abbreviations: LMM: low muscle mass; MA: mild anemia; RERI: relative excess risk due to interaction; ROR: relative odds ratio.

Additive Scale Interaction: We have computed the relative excess risk due to interaction (RERI) to capture interaction on the additive scale. RERI elucidates whether the joint effect of LMM and MA status exceeds the sum of their independent effects.

The RERI is generally calculated using the following formula: $RERI = OR_{11} - OR_{10} - OR_{01} + 1$

Where: OR_{11} is the Odds Ratio for subjects with both risk factors (LMM = Yes and MA = Yes), OR_{10} is the Odds Ratio for subjects with the first risk factor (LMM = Yes) but not the second (MA = No), OR_{01} is the Odds Ratio for subjects with the second risk factor (MA = Yes) but not the first (LMM = No).

$RERI > 0$ indicates a positive additive interaction, $RERI < 0$ indicates a negative additive interaction, and $RERI = 0$ indicates no additive interaction.

The RERI was 0.54 for all-cause mortality, 1.81 for cancer mortality, and 1.70 for noncancer mortality.

Multiplicative Scale Interaction: For the multiplicative scale, we will incorporate the ratio of odds ratios (ROR) to evaluate the interaction on the multiplicative scale. This will indicate whether the joint effect of LMM and MA is different from what would be expected based on their independent effects multiplied together.

Calculating Ratio of Odds Ratios (ROR): $ROR = OR_{11} / (OR_{10} \times OR_{01})$

If $ROR > 1$, the combined effect of both factors is greater than expected under a multiplicative model; If $ROR < 1$, the combined effect of both factors is less than expected.

The ROR was 1.16 for all-cause mortality, 1.87 for cardiovascular mortality, and 1.55 for cancer mortality.

Table S2. Independent and joint association of LMM and MA status with all-cause, cardiovascular, and cancer mortality stratified by age

Study outcome		45~64years (N=7339)		≥65years (N=2974)	
		HR (95% CI)	P value	HR (95% CI)	P value
All-cause mortality					
LMM					
	No	1 (Reference)		1 (Reference)	
	Yes	1.42 (1.11,1.80)	0.005	1.49 (1.30,1.71)	<0.0001
MA					
	No	1 (Reference)		1 (Reference)	
	Yes	1.62 (1.11,2.36)	0.011	1.68 (1.36,2.07)	<0.0001
Joint disease status					
	No condition	1 (Reference)		1 (Reference)	
	LLM only	1.40 (0.92,2.13)	0.111	1.61 (1.25,2.07)	<0.001
	MA only	1.35 (1.04,1.76)	0.024	1.47(1.27,1.69)	<0.0001
	Both conditions	3.88 (1.85,8.13)	<0.001	2.57(1.88,3.51)	<0.0001
Cardiovascular mortality					
LMM					
	No	1 (Reference)		1 (Reference)	
	Yes	1.26 (0.68,2.33)	0.456	1.63 (1.29,2.07)	<0.0001
MA					
	No	1 (Reference)		1 (Reference)	
	Yes	1.87 (0.98,3.58)	0.058	1.68 (1.19,2.37)	0.003
Joint disease status					
	No condition	1 (Reference)		1 (Reference)	
	LLM only	1.30 (0.64, 2.66)	0.473	1.47 (0.91,2.38)	0.116
	MA only	1.10 (0.56, 2.17)	0.780	1.58 (1.23,2.04)	<0.001
	Both conditions	6.19 (2.17,17.67)	<0.001	2.83 (1.74,4.62)	<0.0001
Cancer mortality					
LMM					
	No	1 (Reference)		1 (Reference)	
	Yes	1.68 (1.13,2.50)	0.011	1.75 (1.22,2.50)	0.002
MA					
	No	1 (Reference)		1 (Reference)	
	Yes	0.68 (0.32,1.43)	0.306	2.60 (1.69,4.01)	<0.0001
Joint disease status					
	No condition	1 (Reference)		1 (Reference)	
	LLM only	0.76(0.36,1.61)	0.469	2.23 (1.32,3.76)	0.003
	MA only	1.70 (1.14,2.54)	0.009	1.63 (1.12,2.38)	0.011
	Both conditions	0.18 (0.02,1.51)	0.115	5.05 (2.64,9.67)	<0.0001

Abbreviations: LMM: low muscle mass; MA: mild anemia.

Adjusted for gender, race/ethnicity, marital status, education levels, PIR, body mass index, smoking status, alcohol, consumption, hypertension, diabetes mellitus, hyperlipidemia, ASCVD, CKD, antihypertensive drugs, antidiabetics drugs, antihyperlipidemic drugs.

Table S3. Independent and joint association of LMM and MA status with all-cause, cardiovascular, and cancer mortality stratified by gender

Study outcome		Male (N=5194)		Female (N=5119)	
		HR (95% CI)	P value	HR (95% CI)	P value
All-cause mortality					
LMM					
	No	1 (Reference)		1 (Reference)	
	Yes	1.50 (1.25,1.80)	<0.0001	1.32 (1.11,1.58)	0.001
MA					
	No	1 (Reference)		1 (Reference)	
	Yes	1.85 (1.47,2.34)	<0.0001	1.31 (1.00,1.72)	0.047
Joint disease status					
	No condition	1 (Reference)		1 (Reference)	
	LLM only	1.76 (1.27,2.43)	<0.001	1.27 (0.92,1.74)	0.139
	MA only	1.47 (1.23,1.76)	<0.0001	1.31 (1.09,1.58)	0.004
	Both conditions	2.76 (1.96,3.88)	<0.0001	1.88 (1.06,3.32)	0.031
Cardiovascular mortality					
LMM					
	No	1 (Reference)		1 (Reference)	
	Yes	1.51 (1.08,2.11)	0.016	1.48 (1.10, 1.98)	0.009
MA					
	No	1 (Reference)		1 (Reference)	
	Yes	1.93 (1.33,2.79)	<0.001	1.46 (0.91, 2.36)	0.119
Joint disease status					
	No condition	1 (Reference)		1 (Reference)	
	LLM only	1.62 (0.86,3.04)	0.132	1.26 (0.72, 2.23)	0.417
	MA only	1.42 (0.99,2.03)	0.055	1.43 (1.05, 1.93)	0.022
	Both conditions	2.82 (1.63,4.89)	<0.001	3.37 (1.44, 7.89)	0.005
Cancer mortality					
LMM					
	No	1 (Reference)		1 (Reference)	
	Yes	2.04 (1.44,2.88)	<0.0001	1.22 (0.73,2.01)	0.447
MA					
	No	1 (Reference)		1 (Reference)	
	Yes	2.50 (1.63,3.84)	<0.0001	0.89 (0.45,1.75)	0.737
Joint disease status					
	No condition	1 (Reference)		1 (Reference)	
	LLM only	2.05 (1.15, 3.66)	0.015	0.97 (0.44,2.14)	0.937
	MA only	1.92 (1.35, 2.73)	<0.001	1.24 (0.74,2.06)	0.414
	Both conditions	6.15 (2.84,13.34)	<0.0001	0.68 (0.21,2.15)	0.508

Abbreviations: LMM: low muscle mass; MA: mild anemia

Adjusted for age, race/ethnicity, marital status, education levels, PIR, body mass index, smoking status, alcohol consumption, hypertension, diabetes mellitus, hyperlipidemia, ASCVD, CKD, antihypertensive drugs, antidiabetics drugs, antihyperlipidemic drugs.

Table S4. Joint association of LMM and MA with all-cause, cardiovascular, and cancer mortality among US middle-aged and older adults, NHANES (excluding died within 2 years of follow-up)

Study outcome		Death/No	Weighted death (%)	Hazard ratio (95% CI)		
				Crude model	Model 1	Model 2
All-cause mortality						
LMM	MA					
No	No	1816/5796	7669698 (71.99)	1 (reference)	1 (reference)	1 (reference)
No	Yes	148/300	494498 (4.64)	2.00 (1.61,2.49)	1.53 (1.18,1.99)	1.45 (1.15,1.85)
Yes	No	665/951	2251619 (21.14)	2.32 (2.03,2.66)	1.44 (1.26,1.65)	1.40 (1.21,1.62)
Yes	Yes	71/40	237294 (2.23)	5.49 (3.65,8.27)	2.90 (2.09,4.04)	2.51(1.81,3.48)
P for trend test				<0.0001	<0.0001	<0.0001
Cardiovascular mortality						
LMM	MA					
No	No	587/5796	2291120 (71.39)	1 (reference)	1 (reference)	1 (reference)
No	Yes	41/300	108213 (3.37)	1.55 (1.03, 2.33)	1.27 (0.85, 1.88)	1.17 (0.78,1.76)
Yes	No	217/951	720242 (22.44)	2.75 (2.18, 3.48)	1.64 (1.28, 2.09)	1.40 (1.08,1.83)
Yes	Yes	27/40	89649 (2.79)	7.80 (4.63,13.14)	4.12 (2.11, 8.05)	3.65 (2.21,6.03)
P for trend test				<0.0001	<0.0001	<0.0001
Cancer mortality						
LMM	MA					
No	No	427/5796	1973557 (76.94)	1 (reference)	1 (reference)	1 (reference)
No	Yes	29/300	99554 (3.88)	1.65 (1.06, 2.56)	1.48 (0.96, 2.30)	1.57 (0.99, 2.51)
Yes	No	129/951	452694 (17.65)	2.05 (1.61, 2.62)	1.57 (1.20, 2.06)	1.53 (1.17, 2.01)
Yes	Yes	11/40	39375 (1.53)	4.58 (1.79, 11.71)	2.99 (1.40, 6.42)	3.32 (1.82, 6.07)
P for trend test				<0.0001	<0.0001	<0.0001

Crude model: unadjusted

Model 1: adjusted for age, gender, race/ethnicity, marital status, education levels, PIR, body mass index.

Model 2: adjusted for variables in Model 1 plus smoking status, alcohol consumption, hypertension, diabetes mellitus, hyperlipidemia, ASCVD, CKD, antihypertensive drugs, antidiabetics drugs, antihyperlipidemic drugs.

Abbreviations: NHANES: National Health and Nutrition Examination Survey; LMM: low muscle mass; MA: mild anemia.

Table S5. Association of LMM and MA with cardiovascular and cancer mortality in cause-specific Cox regression models, NHANES 1999 – 2006 and 2011 – 2018

Study outcome	Death/No	Crude model	Hazard ratio (95% CI)		
			Model 1	Model 2	
Cardiovascular mortality					
LMM					
No	684/7885	1 (reference)	1 (reference)	1 (reference)	
Yes	279/1565	2.64 (2.12,3.29)	1.57 (1.26, 1.96)	1.37 (1.07,1.74)	
MA					
No	879/8817	1 (reference)	1 (reference)	1 (reference)	
Yes	84/533	2.18 (1.65,2.88)	1.62 (1.20, 2.18)	1.22 (0.88, 1.68)	
Joint disease status					
No condition	634/7346	1 (reference)	1 (reference)	1 (reference)	
LMM only	50/439	1.72 (1.20,2.45)	1.30 (0.91, 1.84)	1.05 (0.70, 1.59)	
MA only	245/1471	2.50 (1.98,3.14)	1.49 (1.18, 1.87)	1.30 (1.01, 1.67)	
Both conditions	34/94	7.23 (4.59, 11.40)	3.26 (1.93, 5.52)	2.56 (1.54, 4.25)	
Cancer mortality					
LMM					
No	503/7966	1 (reference)	1 (reference)	1 (reference)	
Yes	164/1680	1.96 (1.56,2.47)	1.55 (1.20, 1.99)	1.47 (1.15,1.88)	
MA					
No	616/9080	1 (reference)	1 (reference)	1 (reference)	
Yes	51/566	1.82 (1.21,2.73)	1.59 (1.08,2.33)	1.63 (1.09,2.45)	
Joint disease status					
No condition	468/7512	1 (reference)	1 (reference)	1 (reference)	
LMM only	35/454	1.55 (1.04, 2.32)	1.38 (0.92, 2.06)	1.43 (0.93, 2.20)	
MA only	148/1568	1.88 (1.48, 2.38)	1.49 (1.14, 1.94)	1.42 (1.09, 1.84)	
Both conditions	16/112	4.45 (2.04, 9.72)	2.96 (1.51, 5.82)	3.02 (1.53, 5.94)	

Crude model: unadjusted

Model 1: adjusted for age, gender, race/ethnicity, marital status, education levels, PIR, body mass index.

Model 2: adjusted for variables in Model 1 plus smoking status, alcohol consumption, hypertension, diabetes mellitus, hyperlipidemia, ASCVD, CKD, antihypertensive drugs, antidiabetics drugs, antihyperlipidemic drugs.

Abbreviations: NHANES: National Health and Nutrition Examination Survey; LMM: low muscle mass; MA: mild anemia.

Table S6. Fine – Gray competing risk regression of LMM and MA with mortality, NHANES 1999 – 2006 and 2011 – 2018

Study outcome	Cardiovascular mortality	Cancer mortality	Cardiovascular or Cancer mortality
	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)
LMM			
No	1 (reference)	1 (reference)	1 (reference)
Yes	1.15 (0.98, 1.34)	1.19 (0.97, 1.46)	1.20 (1.06, 1.36)
MA			
No	1 (reference)	1 (reference)	1 (reference)
Yes	0.99 (0.77, 1.27)	1.24 (0.91, 1.69)	1.13 (0.93, 1.39)
Joint disease status			
No condition	1 (reference)	1 (reference)	1 (reference)
LMM only	0.88 (0.65, 1.21)	1.18 (0.82, 1.71)	1.01 (0.79, 1.29)
MA only	1.12 (0.95, 1.32)	1.17 (0.95, 1.45)	1.16 (1.02, 1.33)
Both conditions	1.31 (0.88, 1.95)	1.57 (0.92, 2.68)	1.62 (1.16, 2.26)

Abbreviations: LMM: low muscle mass; MA: mild anemia; SHR: subdistribution hazard ratio.

Adjusted for age, race/ethnicity, marital status, education levels, PIR, body mass index, smoking status, alcohol consumption, hypertension, diabetes mellitus, hyperlipidemia, ASCVD, CKD, antihypertensive drugs, antidiabetics drugs, antihyperlipidemic drugs.

Supplementary Figures

Figure S1 Schoenfeld residual plots of LMM, MA, and their joint presence for testing the proportional hazards assumption

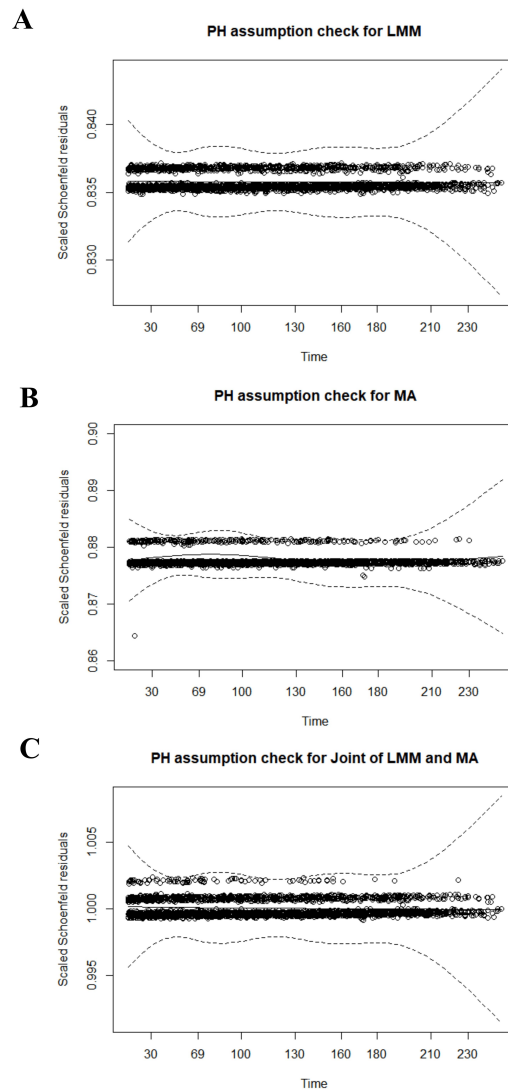


Figure S1 Schoenfeld residual plots of LMM, MA, and their joint presence for testing the proportional hazards assumption. (A) PH assumption for LMM; (B) PH assumption for MA; (C) PH assumption for joint of LMM and MA. Abbreviations: LMM: low muscle mass; MA: mild anemia.