Multimarkers of metabolic malnutrition and inflammation and their association with mortality risk in cardiac catheterisation patients: a prospective, longitudinal, observational, cohort study

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Summary

Background Complex and incompletely understood metabolic dysfunction associated with inflammation and protein–energy wasting contribute to the increased mortality risk of older patients and those with chronic organ diseases affected by cachexia, sarcopenia, malnutrition, and frailty. However, these wasting syndromes have uncertain relevance for patients with cardiovascular disease or people at lower risk. Studies are hampered by imperfect objective clinical assessment tools for these intertwined metabolic malnutrition and inflammation syndromes. We aimed to assess, in two independent cohorts of patients who underwent cardiac catheterisation, the mortality risk associated with the metabolic vulnerability index (MVX), a multimarker derived from six simultaneously measured serum biomarkers plausibly linked to these dysmetabolic syndromes.

Methods In this prospective, longitudinal, observational study, we included patients aged ≥18 years recruited into the CATHGEN biorepository (Jan 2, 2001, to Dec 30, 2011) and the Intermountain Heart Collaborative Study (Sept 12, 2000, to Sept 21, 2006) who underwent coronary angiography and had clinical nuclear magnetic resonance metabolomic profiling done on frozen plasma obtained at catheterisation. We aggregated six mortality risk biomarkers (GlycA, small HDL, valine, leucine, isoleucine, and citrate concentrations) into sex-specific MVX multimarker scores using coefficients from predictive models for all-cause mortality in the CATHGEN cohort. We assessed associations of biomarkers and MVX with mortality in both cohorts using Cox proportional hazards models adjusted for 15 clinical covariates.

Findings We included 5876 participants from the CATHGEN biorepository and 2888 from the Intermountain Heart study. Median follow-up was 6·2 years (IQR 4·4–8·9) in CATHGEN and 8·2 years (6·9–9·2) in the Intermountain Heart study. The six nuclear magnetic resonance biomarkers and MVX made strong, independent contributions to 5-year mortality risk prediction in both cohorts (hazard ratio 2·18 [95% CI 2·03–2·34] in the CATHGEN cohort and 1·67 [1·50–1·87] in the Intermountain Heart cohort). CATHGEN subgroup analyses showed similar MVX associations in men and women, older and younger individuals, for death from cardiovascular or non-cardiovascular causes, and in patients with or without multiple comorbidities.

Interpretation MVX made a dominant contribution to mortality prediction in patients with cardiovascular disease and in low-risk subgroups without pre-existing disease, suggesting that metabolic malnutrition–inflammation syndromes might have a more universal role in survival than previously thought.

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Introduction

In older patients and those with chronic conditions, such as kidney and liver disease, heart failure, chronic obstructive pulmonary disease, rheumatoid arthritis, and cancer, a combination of muscle wasting, malnutrition, and inflammation is a well recognised but incompletely understood syndrome that results in excess mortality risk.[1–3] The unintentional weight loss common to these conditions has been categorised into three primary "overlap syndromes",[3] without clear lines of demarcation between them: cachexia, sarcopenia, and malnutrition.[2,3] The term malnutrition is itself complex and multifaceted, encompassing undernutrition caused by reduced food intake or assimilation, as well as disease-related metabolic derangements resulting in increased resting energy expenditure and muscle catabolism in a context of high systemic inflammation.[1] Among the many descriptors of such syndromes of coexistent protein–energy malnutrition and inflammation is malnutrition–inflammation complex syndrome, used primarily in the clinical context of acute or chronic kidney disease.[4]

Patient subpopulations with a high prevalence of malnutrition–inflammation complex syndrome frequently display a risk factor paradox, also called

Research in context

Evidence before this study

In patients treated with haemodialysis and those with chronic kidney disease, the high mortality risk conferred by a syndrome of intertwined inflammation and protein–energy malnutrition is well recognised, but whether the syndrome influences survival more generally in other patients or the general population has been less investigated. We searched PubMed for papers published from inception to Sept 19, 2022, using the terms "malnutrition–inflammation syndrome" AND "mortality risk", which yielded 100 results, of which 97 had a kidney disease context. An acknowledged limitation of most of these studies and those addressing the metabolic derangements in cachexia, sarcopenia, and frailty is that serum albumin or C-reactive protein concentrations, the laboratory biomarkers usually used to assess these inflammation-related wasting syndromes, are non-specific.

Added value of this study

We developed a composite biomarker score, the metabolic vulnerability index (MVX), derived from six metabolites measured simultaneously by a clinically deployed nuclear magnetic resonance blood test that are likely to reflect different causal aspects of metabolic malnutrition–inflammation syndromes. The MVX score provided strong stratification of all-cause mortality risk in two large, independent cohorts of patients who underwent cardiac catheterisation and were not previously suspected of susceptibility to these dysmetabolic wasting syndromes. The contribution of MVX to multivariable prediction models of 5-year mortality dominated the contributions of 15 risk factors, including age. Risk associations were similarly strong in men and women, in younger and older individuals, those with high and low BMI, and in patients with and without comorbid conditions such as heart failure, renal dysfunction, diabetes, and hypertension. The uniformity of the MVX risk associations in patient subgroups at higher risk and lower risk suggests the influence of metabolic malnutrition–inflammation syndromes on survival might be more universal than previously thought.

Implications of all the available evidence

Our results suggest that survival might be more dependent on previously unrecognised causal factors distinct from those responsible for development of the diseases or vulnerabilities considered to be the causes of death. If supported by future research, treating the underlying metabolic dysfunctions of the overlapping syndromes of cachexia, sarcopenia, malnutrition, and frailty with anti-inflammatory, nutritional, or alternative therapies might provide greater survival benefit than targeting conventional disease risk factors.

reverse epidemiology, whereby increases in conventional cardiovascular risk factors, such as BMI, serum cholesterol, and blood pressure are associated with decreased cardiovascular and all-cause mortality.[5,6] Well established pathophysiological mechanisms contributing to cardiovascular disease are present in these subpopulations, but different superimposed causal factors might drive a reversal of the usual risk factor associations with mortality.[6] Thus, in patients with malnutrition–inflammation complex syndrome, the risk of fatal versus non-fatal outcomes might be driven by different influences, which might be optimally addressed through different therapeutic interventions.

A major impediment to greater awareness and understanding of malnutrition–inflammation complex syndrome and its involvement in frailty, cachexia, and sarcopenia is a dearth of simple quantitative and objective clinical assessment tools.[7–9] The multifaceted malnutrition component is particularly challenging to assess, typically requiring patient history, physical examination, and anthropomorphic measurements.[9] The main biochemical indicators of malnutrition–inflammation complex syndrome are low serum albumin and increased C-reactive protein concentrations, but both are non-specific and thus limited in their clinical applicability.[7,9]

We previously reported that all-cause mortality in the large cohort of cardiovascular patients in the Catheterization Genetics (CATHGEN) study was strongly and independently associated with two biomarkers that might plausibly reflect inflammatory contributions to malnutrition–inflammation complex syndrome.[10,11] Both are measured by nuclear magnetic resonance (NMR) spectroscopy in conjunction with a clinical NMR LipoProfile (Labcorp, Burlington, NC, USA) assessment.[12] The first is GlycA, a composite NMR signal arising from the glycan residues of several acute-phase glycoproteins and thereby providing a sensitive and stable measure of systemic inflammation.[13,14] The second is the quantity of small HDL particles that appear to mediate several protective functions carried out by bound anti-inflammatory and immune response proteins, among others.[10,15]

Since aspects of reverse epidemiology were noted in the CATHGEN cohort (ie, mortality risk inversely associated with hypertension and BMI), we sought to investigate whether any of the small molecule metabolites measured simultaneously with GlycA and small HDL particles by NMR LipoProfile analysis might contribute independently and additively to mortality risk. As we describe, four such metabolites were identified: citrate and the branched-chain amino acids valine, leucine, and isoleucine. We postulate that these six NMR biomarkers reflect, or are manifestations of, the metabolic derangements underlying protein–energy wasting (referred to as metabolic malnutrition) rather than undernutrition aspects of malnutrition and its clinical diagnostic phenotypes.[1] To emphasise this distinction, we will hereafter substitute the term metabolic

malnutrition–inflammation syndrome for malnutrition–inflammation complex syndrome.

We used associations of the six metabolic biomarkers with all-cause mortality in the CATHGEN cohort to derive a mortality risk multimarker score named the metabolic vulnerability index (MVX), as well as two contributing multimarkers called the inflammation vulnerability index (IVX) and metabolic malnutrition index (MMX). We calculated MVX, IVX, and MMX scores for cardiovascular patients in the CATHGEN cohort and assessed the scores' 5-year mortality associations. The findings were replicated in an independent cardiac catheterisation cohort from the Intermountain Heart Collaborative Study.[16]

Methods

Patient data sources and outcomes

The CATHGEN biorepository has been previously described.[17] For this study, we identified consecutive patients (aged ≥18 years) undergoing cardiac catheterisation at Duke University Medical Center (Durham, NC, USA) for suspected ischaemic heart disease and who enrolled in the CATHGEN biorepository between Jan 2, 2001, and Dec 30, 2011, with sufficient available frozen EDTA (edetic acid) plasma. We excluded those with missing angiographic, heart failure, creatinine, and BMI information. Demographics, medical history, and angiographic data were obtained from the Duke Databank for Cardiovascular Disease. Follow-up included assessment of mortality (confirmed through the US National Death Index and the US Social Security Death Index) and myocardial infarction. Every individual was followed up longitudinally, with contact made at 6 months after the procedure and every 12 months thereafter. The CATHGEN biorepository is monitored and was approved by the Duke University institutional review board on March 18, 2011, and included a waiver of authorisation for this study. Before collection of blood samples, all study participants provided written informed consent. Incident events were defined as all-cause or cause-specific death, or non-fatal myocardial infarction at any time during the follow-up period. Time to event was defined as the interval between cardiac catheterisation and death at any point after enrolment. Cardiovascular death was defined as death from one of the following: myocardial infarction, heart failure, sudden death, post-resuscitation, vascular cause, during or after cardiac surgery, or during cardiac catheterisation. Non-cardiovascular death was defined as death due to a non-cardiac medical cause or a non-cardiac cause related to a procedure. Unknown causes of death were defined as unobserved or unknown cause of death. Coronary artery disease was defined as the presence of at least one epicardial coronary vessel with clinically significant stenosis (≥75%) at the time of the index catheterisation.

The second study population was from the Intermountain Heart Collaborative Study cardiac catheterisation registry of patients who underwent coronary angiography (Sept 12, 2000, to Sept 21, 2006) at the LDS Hospital (Salt Lake City, UT, USA).[18] We included consecutive patients aged at least 18 years, who had at least 5 years of follow-up, and sufficient available frozen EDTA plasma. We excluded those with missing clinical (BMI) or laboratory variables (total cholesterol, HDL cholesterol, or creatinine). The study was approved by the Intermountain Urban Central Region institutional review board on March 23, 2012, and the approval included a waiver of authorisation for this study. All patients provided informed consent before undergoing angiography. Incident events were all-cause death assessed by hospital records, Utah State Health Department records (death certificates), and the Social Security Administration death master file. Time to event was defined as the interval between cardiac catheterisation and death at any point after enrolment.

Laboratory assessments

We performed NMR LipoProfile analyses of fasting EDTA plasma samples using the NMR Profiler platform at LipoScience (now Labcorp, Morrisville, NC, USA) with the LP4 algorithm.[19,20] Each scan (proton NMR spectrum) produces particle concentrations of several different-sized subclasses of triglyceride-rich lipoproteins, LDLs, HDLs, mean particle sizes of these lipoprotein classes, plus derived lipids (triglycerides and total cholesterol, LDL cholesterol, and HDL cholesterol),[20] the inflammation marker GlycA,[13] the branched-chain amino acids (valine, leucine, and isoleucine),[21] citrate,[22] plasma protein, ketone bodies, and several other small molecule metabolites.[20] We quantified seven HDL particle subspecies with the indicated estimated diameters: H7P (12·0 nm), H6P (10·8 nm), H5P (10·3 nm), H4P (9·5 nm), H3P (8·7 nm), H2P (7·8 nm), and H1P (7·4 nm).[23] For analysis purposes, we grouped these subspecies into small-HDL particle (H1P plus H2P plus H3P) and large-HDL particle (H4P plus H5P plus H6P plus H7P) subclasses. We measured lipids and creatinine by standardised chemical analysis, and estimated glomerular filtration rate was calculated with the 2021 CKD-EPI equation. Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 mL/min per 1·73 m².

Statistical analysis

Continuous variables are presented as mean (SD) or median (IQR), and categorical variables as percentages. We used the χ^2 statistic and student's t test to compare baseline characteristics among those who did and did not die during a 5-year follow-up period. We used Spearman correlation coefficients to assess correlations between selected variables. We computed cumulative mortality incidence curves for subgroups of baseline MVX values. We assessed associations of NMR-measured lipoprotein and metabolite variables with all-cause mortality (and additionally cause-specific mortality and non-fatal

myocardial infarction in the CATHGEN cohort) using Cox proportional hazards models adjusted for age, sex, race, smoking, diabetes, hypertension, BMI, total cholesterol, HDL cholesterol, triglycerides, estimated glomerular filtration rate, coronary artery disease, heart failure, previous myocardial infarction, and family history of coronary artery disease. We restricted longevity modelling to a 5-year time horizon, arguably of most clinical interest, with sensitivity analyses in CATHGEN examining timeframes of 1 year, 3 years, and more than 5 years. We tested the assumption of proportional hazards by including time-varying covariates in the models. Among several NMR measures found to have statistically significant associations with all-cause mortality in CATHGEN when examined individually, including plasma protein (inverse) and ketone bodies, only six (small HDL particles, GlycA, citrate, valine, leucine, and isoleucine) made significant independent contributions to a joint prediction model. We combined these measures into sex-specific IVX, MMX, and MVX multimarker scores (appendix p 1). Estimates of the relative importance of each predictive variable were provided by its χ^2 value as a percentage of the total χ^2 of the model. These estimates were similar to those derived by comparing the Harrell's C-index of the full model with those of models leaving out each variable. All reported p values are two-sided.

See Online for appendix

	CATHGEN biorepository (n=5876)			Intermountain Heart study (n=2888)		
	Alive (n=4876)	Died (n=1000)	p value	Alive (n=2447)	Died (n=441)	p value
Demographics						
Age, years	59·6 (11·3)	65·1 (11·5)	<0·0001	62·5 (11·8)	70·7 (11·7)	<0·0001
Sex						
Male	3027 (62·1%)	652 (65·2%)	0·063	1611 (65·8%)	290 (65·8%)	0·98
Female	1849 (37·9%)	348 (34·8%)	0·063	836 (34·2%)	151 (34·2%)	0·98
Race or ethnicity						
White	3689 (75·7%)	744 (74·4%)	0·40	2217 (90·6%)	399 (90·5%)	0·93
Black	913 (18·7%)	200 (20·0%)	0·35	14 (0·6%)	5 (1·1%)	0·20
Native American	132 (2·7%)	33 (3·3%)	0·30	9 (0·4%)	0 (0·0%)	0·37
Other or unknown	142 (2·9%)	23 (2·3%)	0·29	207 (8·5%)	37 (8·4%)	1·00
Comorbidities and risk factors						
Hypertension	3345 (68·6%)	672 (67·2%)	0·39	1599 (65·4%)	332 (75·3%)	<0·0001
Smoking	2236 (45·9%)	536 (53·6%)	<0·0001	411 (16·8%)	85 (19·3%)	0·20
Diabetes	1308 (26·8%)	361 (36·1%)	<0·0001	595 (24·3%)	161 (36·5%)	<0·0001
BMI, kg/m²	30·4 (7·2)	28·9 (7·2)	<0·0001	29·8 (6·9)	28·6 (6·5)	<0·0001
Family history of coronary artery disease	1613 (33·1%)	297 (29·7%)	0·038	1137 (46·5%)	165 (37·4%)	0·0004
Heart failure	1151 (23·6%)	405 (40·5%)	<0·0001	329 (13·5%)	152 (34·5%)	<0·0001
Chronic kidney disease	949 (19·5%)	388 (38·8%)	<0·0001	510 (20·8%)	209 (47·4%)	<0·0001
Previous myocardial infarction	1212 (24·9%)	308 (30·8%)	0·0002	315 (12·9%)	79 (17·9%)	0·0045
Coronary artery disease on angiography	2757 (56·6%)	644 (64·4%)	<0·0001	1565 (64·0%)	330 (74·8%)	<0·0001
Laboratory biomarkers						
Total cholesterol, mmol/L	3·9 (0·9)	3·8 (1·0)	0·0019	4·5 (1·1)	4·2 (1·2)	<0·0001
Triglycerides, mmol/L	1·1 (0·7–1·6)	0·9 (0·6–1·5)	<0·0001	1·5 (1·1–2·1)	1·4 (1·0–2·0)	0·14
HDL cholesterol, mmol/L	1·14 (0·31)	1·12 (0·35)	0·15	1·06 (0·33)	1·03 (0·37)	0·075
eGFR, mL/min per 1·73 m²	78·2 (21·8)	66·9 (27·2)	<0·0001	76·7 (21·8)	60·8 (25·7)	<0·0001
GlycA, µmol/L	365 (319–420)	396 (346–466)	<0·0001	333 (276–402)	368 (297–447)	<0·0001
Small HDL particles, µmol/L	13·4 (11·3–15·4)	11·1 (8·8–13·4)	<0·0001	13·0 (10·7–15·2)	11·0 (8·5–14·0)	<0·0001
Leucine, µmol/L	128 (107–151)	114 (90–138)	<0·0001	131 (111–154)	118 (96–145)	<0·0001
Valine, µmol/L	198 (170–224)	178 (147–213)	<0·0001	204 (174–239)	183 (153–220)	<0·0001
Isoleucine, µmol/L	68 (58–80)	68 (55–80)	0·084	67 (55–79)	64 (53–78)	0·071
Citrate, µmol/L	102 (85–122)	112 (89–134)	<0.0001	107 (88–130)	116 (93–145)	<0.0001
IVX score*	48 (40–57)	60 (50–71)	<0·0001	47 (38–56)	56 (45–67)	<0·0001
MMX score*	49 (43–55)	55 (48–63)	<0·0001	49 (45–55)	54 (48–62)	<0·0001
MVX score*	48 (40–56)	60 (51–68)	<0·0001	48 (41–55)	58 (49–66)	<0·0001

Data are n (%), mean (SD), or median (IQR). eGFR=estimated glomerular filtration rate. IVX=inflammation vulnerability index. MMX=metabolic malnutrition index. MVX=metabolic vulnerability index. *Score range 1–100.

Table 1: **Baseline characteristics of the CATHGEN biorepository and Intermountain Collaborative Heart study cardiac catheterisation cohorts**

CATHGEN statistical analyses were done by author IS using SAS (version 9.4) and Intermountain Heart statistical analyses were done by HTM using SPSS (version 22.0).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From the CATHGEN biorepository, we identified 6969 eligible patients, of whom we excluded 1093 participants with missing angiographic (n=889 [12·8%]), heart failure (n=98 [1·4%]), creatinine (n=78 [1·1%]) and BMI (n=28 [0·4%]) data. From the Intermountain Heart cohort, we identified 2998 patients, of whom we excluded 110 (3·7%) participants with one or more missing values for BMI, total cholesterol, HDL cholesterol, or creatinine. 1000 (17·0%) of 5876 CATHGEN patients (median follow-up was 6·2 years [IQR 4·4–8·9]) and 441 (15·3%) of 2888 Intermountain Heart patients (median follow-up was 8·2 years [6·9–9·2]) died within 5 years. 746 (12·7%) patients in the CATHGEN cohort and 154 (5·3%) patients in the Intermountain Heart study were censored during the 5-year study period due to loss to follow-up.

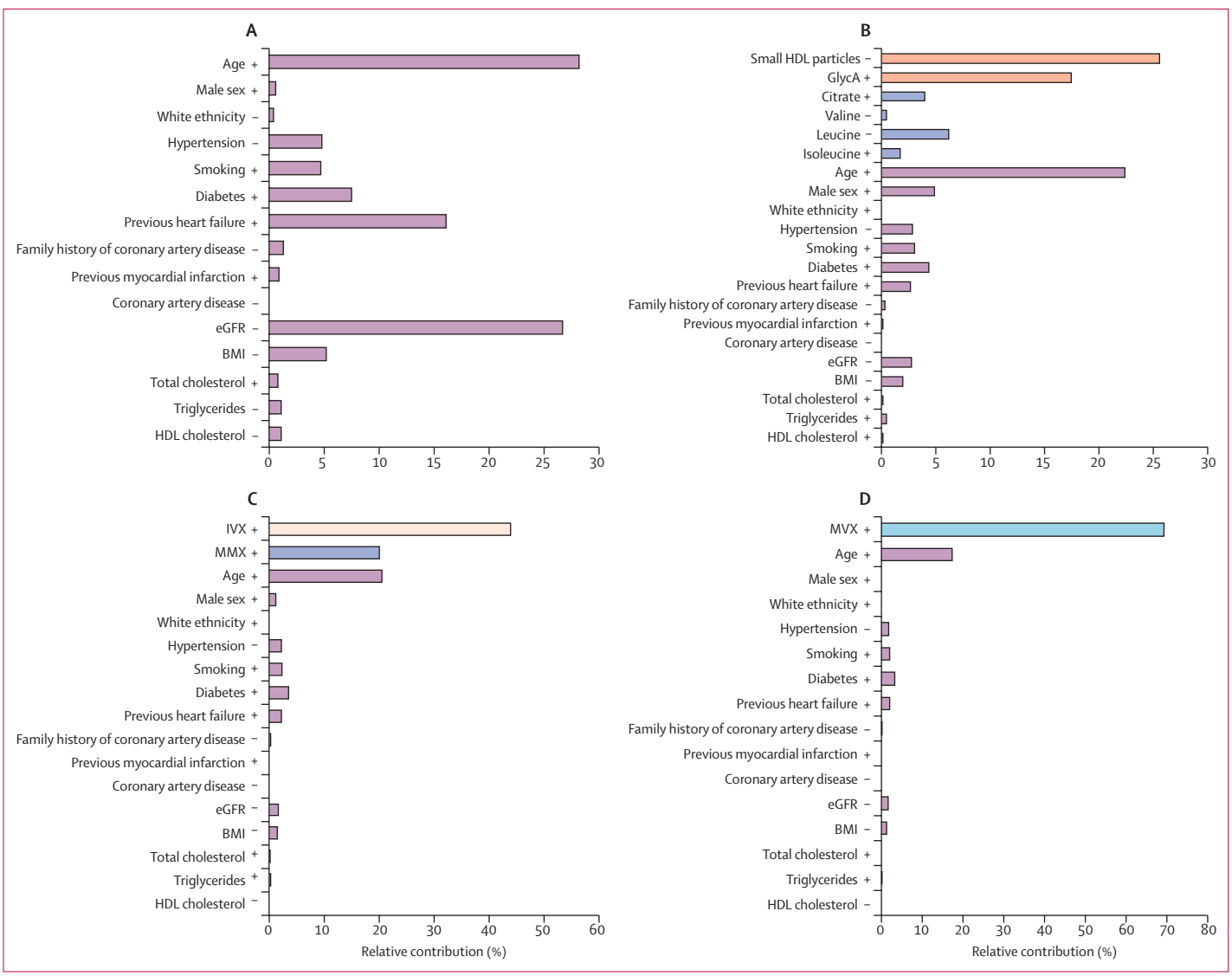


Figure 1: **Relative contribution of each variable to predictive models of 5-year all-cause mortality in the CATHGEN cohort**

Data are shown as the percentage contribution made by the χ^2 value of each variable to the total χ^2 of the Cox regression model. The plus and minus signs indicate whether the mortality association of the indicated variable is positive or negative. (A) The base model that includes the 15 clinical covariates. (B) The base model to which the six nuclear magnetic resonance biomarkers were added. (C) The base model to which the IVX and MMX multimarker score variables were added. (D) The base model to which the MVX multimarker score was added. eGFR=estimated glomerular filtration rate. IVX=inflammation vulnerability index. MMX=metabolic malnutrition index. MVX=metabolic vulnerability index.

	First quintile	Second quintile	Third quintile	Fourth quintile	Fifth quintile	HR (95% CI) per SD
CATHGEN cohort						
IVX score	<38·7	38·7–46·1	46·2–53·3	53·4–62·3	≥62·4	..
Events/N (%)	64/1169 (5·5%)	110/1164 (9·5%)	152/1170 (13·0%)	235/1183 (19·9%)	439/1190 (36·9%)	..
HR (95% CI)	1·00 (reference)	1·72 (1·27–2·35)	2·20 (1·64–2·95)	3·37 (2·55–4·76)	6·66 (5·07–8·73)	1·93 (1·80–2·07)
MMX score	<42·7	42·7–47·3	47·4–52·0	52·1–58·1	≥58·2	..
Events/N (%)	97/1163 (8·3%)	125/1174 (10·7%)	160/1180 (13·6%)	212/1170 (18·1%)	406/1189 (34·2%)	..
HR (95% CI)	1·00 (reference)	1·28 (0·98–1·67)	1·52 (1·18–1·96)	1·99 (1·56–2·54)	3·61 (2·87–4·54)	1·56 (1·47–1·66)
MVX score	<39·5	39·5–46·5	46·6 – 52·7	52·8–60·6	≥60·7	..
Events/N (%)	54/1164 (4·6%)	91/1167 (7·8%)	156/1162 (13·4%)	227/1199 (18·9%)	472/1184 (39·9%)	..
HR (95% CI)	1·00 (reference)	1·60 (1·14–2·25)	2·64 (1·93–3·60)	3·50 (2·59–4·73)	8·01 (5·99–10·70)	2·18 (2·03–2·34)
Intermountain Heart study cohort						
IVX score	≤37·5	37·6–44·4	44·5–52·4	52·5–61·5	≥61·6	..
Events/N (%)	51/578 (8·8%)	46/578 (8·0%)	71/574 (12·4%)	86/578 (14·9%)	187/580 (32·2%)	..
HR (95% CI)	1·00 (reference)	0·76 (0·51–1·13)	1·12 (0·78–1·61)	1·24 (0·87–1·77)	2·42 (1·73–3·38)	1·50 (1·34–1·67)
MMX score	≤42·6	42·7–47·2	47·3–51·6	51·7–58·0	≥58·1	..
Events/N (%)	51/579 (8·8%)	58/577 (10·1%)	73/577 (12·7%)	98/579 (16·9%)	161/576 (28·0%)	..
HR (95% CI)	1·00 (reference)	1·18 (0·81–1·72)	1·38 (0·97–1·98)	1·59 (1·13–2·24)	2·23 (1·62–3·09)	1·32 (1·21–1·44)
MVX score	≤38·4	38·5–52·3	52·4–52·0	52·1–59·8	≥59·9	..
Events/N (%)	41/574 (7·1%)	46/582 (7·9%)	53/574 (9·2%)	107/577 (18·5%)	194/581 (33·4%)	..
HR (95% CI)	1·00 (reference)	0·89 (0·58–1·36)	0·95 (0·63–1·44)	1·64 (1·13–2·37)	2·72 (1·91–3·89)	1·67 (1·50–1·87)

HRs and 95% CIs are from Cox proportional hazard regression models adjusted for age, sex, race, smoking, diabetes, hypertension, BMI, total cholesterol, HDL cholesterol, triglycerides, estimated glomerular filtration rate, coronary artery disease, heart failure, previous myocardial infarction, and family history of coronary artery disease. In the CATHGEN cohort, the SD is 14·0 for IVX, 9·8 for MMX, and 12·7 for MVX. In the Intermountain Heart Collaborative Study cohort, the SD is 14·2 for IVX, 9·6 for MMX, and 12·5 for MVX. HR=hazard ratio. IVX=inflammation vulnerability index. MMX=metabolic malnutrition index. MVX=metabolic vulnerability index

Table 2: **Associations of IVX, MMX, and MVX with 5-year mortality in the CATHGEN and Intermountain Heart Collaborative Study cohorts**

In both cohorts, we found a high prevalence of hypertension, diabetes (of any type), heart failure, chronic kidney disease, and angiographically defined coronary artery disease, as well as signs of the risk factor paradox (lower cholesterol, triglycerides, and BMI in patients who died compared with those who did not die; table 1). Among the NMR-measured metabolites postulated to reflect metabolic malnutrition–inflammation syndrome, concentrations of GlycA and citrate were higher and concentrations of small HDL particles, valine, and leucine were lower in patients who died than in those who did not die (table 1). Spearman correlations between these biomarkers and with selected risk factors were similar in both cohorts (appendix p 2).

In the CATHGEN cohort, the six postulated metabolic malnutrition–inflammation syndrome biomarkers made significant contributions to a multivariable prediction model of mortality, increasing the discrimination C-index of the base model (covariates) substantially, from 0·690 to 0·761 (figure 1A, B; appendix pp 3–4). As estimated by the percentual contribution made to the total χ^2 of the model, the strongest base model predictors were age (28%), renal function assessed by estimated glomerular filtration rate (27%), heart failure (16%), and diabetes (8%; figure 1A). Addition of the metabolic malnutrition–inflammation syndrome biomarkers to the model substantially reduced the predictive contributions of heart failure and estimated glomerular filtration rate (to 3% each), which were replaced in importance by small HDL particles (25%) and GlycA (17%; figure 1B). The strong protective (inverse) association observed for small HDL particles applied only to particles smaller than about 8·8 nm diameter; concentrations of large HDL particles and total HDL cholesterol had negligible mortality associations (appendix p 7). In the Intermountain Heart replication cohort, associations between the six metabolic malnutrition–inflammation syndrome variables and mortality were similar to those in the CATHGEN cohort, but the relative contributions of small HDL particles (12%) and GlycA (12%) were comparatively lower and those of heart failure (9%) and estimated glomerular filtration rate (13%) comparatively greater (appendix p 16).

Given the complexity and multifactorial cause of the metabolic dysfunctions underlying cachexia, sarcopenia, and malnutrition and its associated mortality risk, we produced two mortality multimarker subscores: IVX, combining GlycA and small HDL particles, and MMX, combining valine, leucine, isoleucine, and citrate (appendix p 1). We calculated sex-specific scores to make scores numerically similar in men and women, which they would not be otherwise owing to sex differences in metabolite levels unrelated to mortality risk (citrate and GlycA concentrations are higher and branched-chain

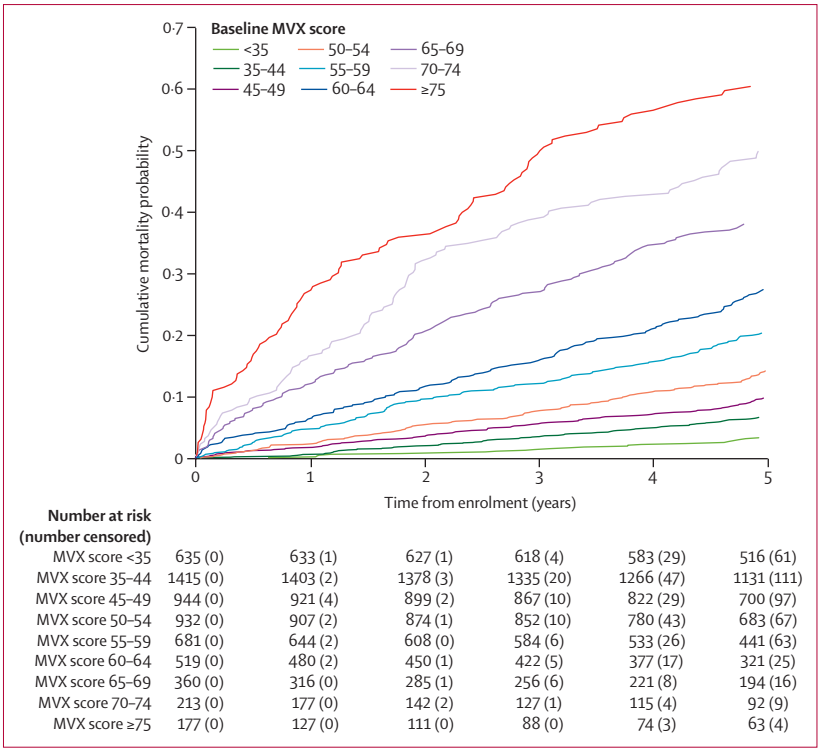
amino acid levels lower in women than in men; appendix p 8).

In the CATHGEN cohort, the predictive contribution of IVX (44%) was about twice that of MMX (20%; figure 1C; appendix p 5), whereas in the Intermountain Heart cohort, the IVX and MMX mortality risk contributions were more similar (18% and 12%; appendix p 16). By contrast with mortality prediction, we found in the CATHGEN cohort that the risk of non-fatal myocardial infarction was much less influenced by the metabolic malnutrition–inflammation syndrome-related NMR biomarkers and much more dependent on comorbid conditions, with the combination of prevalent angiographic coronary artery disease and previous history of myocardial infarction making dominant contributions (62–75%; appendix pp 3–6).

We combined IVX and MMX to produce the MVX score. The calculation of MVX includes a product term (IVX×MMX) accounting for observed interaction (synergy) between the putative inflammation and metabolic malnutrition elements of malnutrition–inflammation complex syndrome (appendix p 1). A cross-classification graph of 5-year mortality by IVX and MMX tertile (appendix p 17) illustrates this interaction by showing that higher mortality risk in those with high MMX scores occurs only when IVX scores are also high. MVX scores in the CATHGEN cohort contributed far more to mortality prediction (69%) than did any of the other 15 risk factors in the model, including age (17%; figure 1D; appendix p 6). In the Intermountain Heart study cohort, MVX score was also dominant, although less so, with its predictive contribution (31%) exceeding those of all variables except age (35%; appendix p 16).

We found a deviation of the assumption of proportional hazards ($p<0·0001$) in models of 5-year mortality for IVX and MVX scores, but not MMX score. We therefore did a sensitivity analysis that compared models limited to death within 1 year (n=255), 3 years (n=651), and 5 years (n=1000), or after 5 years (n=529) of enrolment in CATHGEN (appendix pp 9–10). IVX and MVX scores were associated most strongly with 1-year mortality (hazard ratio [HR] 2·48 [95% CI 2·13–2·89] for IVX and 3·00 [2·60–3·45] for MVX), and remained dominant predictors of death after 5 years (1·57 [1·42–1·72] for IVX and 1·53 [1·39–1·68] for MVX). MMX, by contrast, displayed near constant mortality associations for the first 5 years of follow-up, which weakened substantially in the longer term. The contributions of MVX score (82%) and age (10%) dominated prediction of 1-year mortality and remained important for death occurring after 5 years (36% for MVX and 42% for age).

The significant mortality associations of all three multimarkers in the CATHGEN cohort were replicated in the Intermountain Heart study cohort, but were weaker (table 2). A plot of cumulative mortality in subgroups of CATHGEN participants stratified by small differences in baseline MVX score shows a remarkably graded relationship, with clinically meaningful mortality differences seen not just for high values, but also lower MVX scores (figure 2). Risk stratification by MVX quintile in the Intermountain Heart study cohort was similar to that observed in the CATHGEN cohort (appendix p 18).



Number at risk (number censored)						
MVX score <35	635 (0)	633 (1)	627 (1)	618 (4)	583 (29)	516 (61)
MVX score 35–44	1415 (0)	1403 (2)	1378 (3)	1335 (20)	1266 (47)	1131 (111)
MVX score 45–49	944 (0)	921 (4)	899 (2)	867 (10)	822 (29)	700 (97)
MVX score 50–54	932 (0)	907 (2)	874 (1)	852 (10)	780 (43)	683 (67)
MVX score 55–59	681 (0)	644 (2)	608 (0)	584 (6)	533 (26)	441 (63)
MVX score 60–64	519 (0)	480 (2)	450 (1)	422 (5)	377 (17)	321 (25)
MVX score 65–69	360 (0)	316 (0)	285 (1)	256 (6)	221 (8)	194 (16)
MVX score 70–74	213 (0)	177 (0)	142 (2)	127 (1)	115 (4)	92 (9)
MVX score ≥75	177 (0)	127 (0)	111 (0)	88 (0)	74 (3)	63 (4)

Figure 2: **Kaplan-Meier cumulative mortality incidence curves for subgroups of patients in the CATHGEN cohort with differing baseline metabolic vulnerability index scores**
MVX=metabolic vulnerability index.

Of the 1000 deaths that occurred within 5 years in the CATHGEN cohort, 379 (38%) were from cardiovascular causes, 507 (51%) were from non-cardiovascular causes, and 114 (11%) were of unknown cause (appendix pp 11–12). Whereas some risk factors such as heart failure and diabetes predicted cardiovascular death but not non-cardiovascular death, IVX, MMX, and MVX scores were similarly related to mortality risk irrespective of cause (for cardiovascular death, MVX HR 2·02 [95% CI 1·80–2·26], IVX 1·75 [1·57–1·97], and MMX 1·35 [1·23–1·48]; for non-cardiovascular death, MVX 2·30 [2·08–2.53], IVX 1·92 [1·74–2·13], and MMX 1·40 [1·29–1·52]).

MVX score associations with all-cause mortality were similar in men and women and in those with and without risk factors that affected 5-year survival rates (table 3; appendix pp 13–15). Notably, the MVX score predicted mortality similarly well in patients who had differences in death rates of nearly two times, such as those with and without heart failure or chronic kidney disease or in the lowest (<22 kg/m²) versus highest (≥30 kg/m²) BMI categories. MVX mortality associations were the strongest in the two lowest-risk patient subgroups: the youngest

	Deaths	MVX score	HR per 1 SD (95% CI)	HR Q5 *vs* Q1 (95% CI)
All patients	1000/5876 (17·0%)	50·1 (12·7)	2·18 (2·03–2·34)	8·01 (5·99–10·70)
Men	652/3679 (17·7%)	50·2 (13·2)	2·18 (1·99–2·38)	8·29 (5·75–11·93)
Women	348/2197 (15·8%)	50·0 (11·8)	2·22 (1·97–2·50)	8·56 (5·23–13·99)
Age, years				
≤50	113/1162 (9·7%)	49·1 (13·0)	2·61 (2·10–3·24)	12·79 (5·05–32·40)
51–60	213/1776 (12·0%)	48·6 (12·5)	2·39 (2·06–2·77)	11·62 (5·58–24·22)
61–70	340/1701 (20·0%)	50·5 (12·9)	2·12 (1·87–2·39)	6·87 (4·41–10·72)
>70	334/1237 (27·0%)	52·8 (11·9)	1·90 (1·67–2·16)	4·72 (3·03–7·34)
BMI, kg/m^2				
<22	131/443 (29·6%)	56·4 (12·2)	1·96 (1·58–2·42)	5·95 (2·83–12·51)
22–29·9	519/2925 (17·7%)	50·1 (13·1)	2·27 (2·05–2·52)	12·75 (7·81–20·81)
≥30	350/2508 (14·0%)	49·1 (12·0)	2·01 (1·78–2·26)	5·30 (3·40–8·26)
Hypertension				
Yes	672/4017 (16·7%)	50·0 (12·6)	2·02 (1·85–2·20)	5·99 (4·31–8·34)
No	328/1859 (17·6%)	50·4 (12·9)	2·44 (2·15–2·77)	14·05 (7·73–25·55)
Smoking				
Yes	536/2772 (19·3%)	50·4 (12·7)	2·10 (1·90–2·32)	6·95 (4·75–10·17)
No	464/3104 (15·0%)	49·8 (12·6)	2·28 (2·06–2·53)	9·48 (6·05–14·84)
Diabetes				
Yes	361/1669 (21·6%)	51·7 (12·5)	2·04 (1·81–2·29)	6·24 (4·02–9·69)
No	639/4207 (15·2%)	49·5 (12·7)	2·25 (2·05–2·46)	9·39 (6·39–13·79)
Heart failure				
Yes	405/1556 (26·0%)	54·4 (13·2)	1·95 (1·74–2·20)	5·54 (3·69–8·31)
No	595/4320 (13·8%)	48·6 (12·1)	2·33 (2·13–2·55)	10·68 (7·16–15·94)
Previous myocardial infarction				
Yes	308/1520 (20·3%)	52·1 (12·6)	2·03 (1·77–2·33)	7·40 (4·32–12·67)
No	692/4356 (15·9%)	49·4 (12·6)	2·24 (2·06–2·43)	9·67 (6·74–13·88)
Coronary artery disease				
Yes	644/3402 (18·9%)	50·5 (12·6)	2·10 (1·92–2·30)	7·23 (5·06–10·33)
No	356/2474 (14·4%)	49·5 (12·7)	2·30 (2·04–2·59)	8·31 (5·17–13·36)
Chronic kidney disease				
Yes	388/1337 (29·0%)	55·5 (12·9)	1·99 (1·76–2·25)	5·71 (3·78–8·62)
No	612/4539 (13·5%)	48·5 (12·2)	2·25 (2·06–2·45)	8·79 (6·06–12·74)
No coronary artery disease, no heart failure, no diabetes, and no chronic kidney disease	130/1208 (10·8%0	46·8 (12·2)	2·67 (2·18–3·28)	11·44 (4·52–28·94)

Data are n/N (%) or mean (SD), unless otherwise indicated. HRs and 95% CIs per 1 SD and for the top (Q5) versus bottom (Q1) quintiles are from Cox proportional hazards models adjusted for age, sex, race, smoking, diabetes, hypertension, BMI, total cholesterol, HDL cholesterol, triglycerides, estimated glomerular filtration rate, angiographic coronary artery disease, heart failure, previous myocardial infarction, and family history of coronary artery disease. HR=hazard ratio. MVX=metabolic vulnerability index.

***Table 3*: Associations of MVX with 5-year mortality in CATHGEN patient subgroups**

(aged ≤50 years) and those without coronary artery disease, heart failure, diabetes, or chronic kidney disease (table 3).

Discussion

We used clinical NMR analysis to efficiently quantify six metabolites in plasma plausibly related to metabolic malnutrition–inflammation syndrome and found that derived IVX, MMX, and MVX multimarker scores exhibited strong, graded associations with all-cause mortality in two large cardiac catheterisation cohorts. The associations were similarly strong in men and women, younger and older patients, those with low BMI and high BMI, for death from cardiovascular and non-cardiovascular causes, and in patients with and without angiographic evidence of coronary artery disease or other comorbid conditions such as heart failure, renal dysfunction, diabetes, and hypertension. These observations and the finding that MVX mortality associations were particularly strong in the two lowest-risk patient subgroups—those aged 50 years and younger and those without coronary artery disease, heart failure, chronic kidney disease, or diabetes—suggest that metabolic malnutrition–inflammation syndrome might have general relevance to mortality risk by predisposing to metabolic vulnerability or resilience.

Our hypothesis that previously unsuspected metabolic factors might have a large effect on the probability of a patient living to a more advanced age or surviving the various chronic diseases that are major causes of death has potentially important preventive implications (figure 3). A similar hypothesis was previously advanced to explain reverse epidemiology in patients treated with haemodialysis and other vulnerable patient subpopulations, and the poor results of prevention efforts to improve survival that focused on conventional risk factors such as obesity, hypertension, and hypercholesterolaemia.[5,6] Our findings in a patient subpopulation that was not previously linked to malnutrition–inflammation syndromes suggest a degree of biological universality to the contribution the associated metabolic dysfunctions make to mortality risk. Particularly noteworthy was the dominance of the predictive contribution of MVX scores to multivariable models of 5-year mortality, exceeding (in the CATHGEN cohort) or similar to (in the Intermountain Heart study cohort) that of age, and surpassing the importance of such established risk factors as smoking, diabetes, heart failure, and renal function. Together, these variables in the CATHGEN cohort accounted for more than half of the mortality prediction of a Cox model that did not include MVX score. However, the addition of MVX score to the model greatly attenuated the mortality risks from heart failure and renal dysfunction, suggesting a largely metabolic basis for these associations, and overall mortality prediction improved so substantially that the predictive contribution of MVX dwarfed those of the covariates. By contrast, risk of non-fatal myocardial infarction was little influenced by the MVX score and its component parts.

If metabolic malnutrition–inflammation syndrome has a key role in the short-term survival of cardiovascular patients, then the customary use of composite endpoints that combine fatal and non-fatal events in clinical trials of atherosclerotic cardiovascular disease should be questioned. Previous critiques of composite endpoints have centred on the pitfalls of clinical interpretation and the weighting of hard and soft outcomes,[24] but have never questioned the foundational assumption that fatal and non-fatal atherosclerotic cardiovascular disease events

share a common cause. Such events unquestionably do, but if a more potent metabolic malnutrition–inflammation syndrome cause is superimposed and dominates survival (figure 3), it would explain why MVX score had an over-riding influence on both cardiovascular and non-cardiovascular mortality, but far less on non-fatal myocardial infarction. Viewed through this lens, the results of past clinical trials in which the interventions had unequal effects on the fatal and non-fatal components of the composite endpoint might merit re-examination.

Given the remarkably strong mortality associations of MVX score and its MMX and IVX score component parts, why has the importance of metabolic dysfunctions associated with syndromes of systemic inflammation and malnutrition largely been unrecognised in clinical practice and research. The main reason is a paucity of clinically accessible serum markers that are specific to the detection of coexistent protein–energy malnutrition and inflammation.[7,9] As noted in consensus reports, the development of new biomarkers enabling early detection and intervention is a high priority.[1–3] The challenge is the inherent complexity of the overlap syndromes, with uncertainty as to which of the intertwined metabolic stresses are causes versus manifestations.[4,25] Included among these stresses are chronic inflammation, endocrine disorders, oxidative stress, protein hypercatabolism, acidaemia, muscle anabolic resistance, defective mTOR signalling, increased resting energy expenditure, and endothelial dysfunction.[4,25,26] In light of this complexity, the MVX multimarker score that aggregates six simultaneously measured metabolites that are likely to reflect different aspects of the syndrome might unsurprisingly have advantages over serum albumin and C-reactive protein, the usual clinical markers. The splitting of the MVX score into the IVX and MMX component parts served the potential future clinical purpose of treating metabolic malnutrition–inflammation syndrome-related mortality risk differentially depending on the reasons underlying increased MVX score. We recognise, however, the arbitrary nature of ascribing IVX scores to inflammatory causes and MMX scores to metabolic malnutrition causes, given their apparent synergy and uncertainty about how branched-chain amino acids and citrate, in particular, are mechanistically involved.[27–29]

The major influence of small HDL particles on IVX and MVX scores is particularly intriguing. Understanding how this small HDL subspecies is involved with metabolic malnutrition–inflammation syndrome might help identify which aspects of HDL multifunctionality affect longevity and metabolic resilience.[15,30] Perceptions of the clinical importance of HDL are based almost exclusively on studies of just one HDL biomarker: HDL cholesterol. Because the amount of cholesterol per particle in large HDL subpopulations far exceeds that in small HDL subpopulations, clinical associations of HDL cholesterol can mislead about the protective role played by small HDL particles.[10,30] The present study offers an informative example: HDL cholesterol added to a multivariable model for mortality in CATHGEN did not increase the C-index, whereas addition instead of small HDL particles increased the C-index substantially. Concentrations of large HDL particles had no association with mortality. This sharp particle-size demarcation of apparent HDL biological activity is consistent with evidence that certain HDL functional activities such as anti-oxidation, anti-inflammation, and anti-infection are mediated by proteins or lipid species that reside preferentially or exclusively on small-size HDL particle subpopulations.[15,30]

Anticipating how MVX and its component MMX and IVX scores will ultimately be used in clinic might be premature, but several possibilities invite future research. The MVX score has clear mortality prognostic value, but whether lowering MVX score by anti-inflammatory, nutritional, or alternative therapies would extend survival is not known. The best clinical fit for MVX might be to complement or extend the "disease burden/inflammation" as one of five criteria recommended by Cederholm and colleagues[1] for diagnosing and grading the severity of malnutrition as it relates to the syndromes of cachexia, sarcopenia, and frailty.[1–3,8] In this context, the MVX score could furnish a simple, quantitative, and objective measure of the metabolic dysfunction affecting

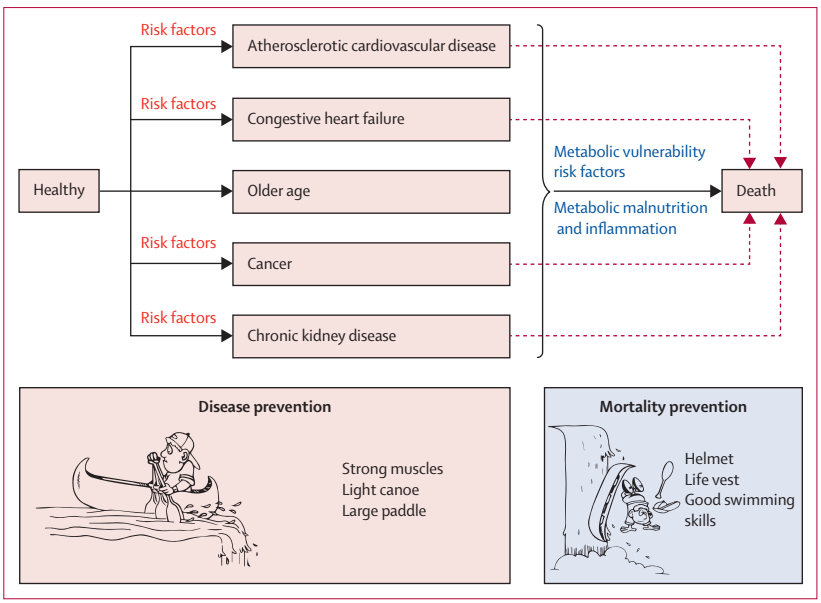


***Figure 3*: Conceptual representation of different clinical considerations that might apply to disease prevention and mortality prevention**

The top left of the figure depicts long-term trajectories to conditions such as atherosclerotic cardiovascular disease, heart failure, cancer, and chronic kidney disease, influenced by disease-specific risk factors that also serve as targets for prevention, such as high cholesterol for atherosclerotic cardiovascular disease. The bottom left presents an analogy of a canoeist using the most pertinent tools (eg, strong muscles) to avoid being swept over the waterfall. Depicted on the top right is the suggestion that later in the trajectory, when mortality is more proximal, the dominant risk factors are those related to metabolic vulnerability. The canoeist under these altered circumstances would gain a survival benefit from using a different set of prevention tools (eg, a helmet), highlighting differences between potential strategies to prevent disease versus extending survival from disease or advanced age.

survival for which there is an unmet need, both for prognosis and to aid investigation of the efficacy and safety of therapeutic interventions. In terms of real-world clinical practicality, because the analysis uses no assay-specific reagents or other consumables, MVX, IVX, and MMX indices could be produced at little or no incremental analytic cost with data from the same NMR LipoProfile scan used in the USA for routine patient testing for cardiometabolic risk via simultaneous assessment of the lipid panel, apolipoprotein B, GlycA, and lipoprotein insulin resistance score.[12,13,20]

A major strength of our study is that independent analyses were done in two large, prospective cardiovascular patient cohorts with detailed clinical characteristics and outcomes gathered during long-term follow-up. However, an important limitation is the inherent selection bias introduced by restricting the cohorts to patients presenting for suspected ischaemic heart disease, limiting the generalisability of results. Details are also lacking about causes of non-cardiovascular death. Because branched-chain amino acid concentrations vary depending on meal composition, nutritional state, and length of fasting, not having this information might confound interpretation of the magnitudes of the MMX mortality associations. For this and other reasons, the equations used to calculate the IVX, MMX, and MVX scores should be considered provisional, pending evaluation in other, more general populations. Another limitation is that, to facilitate potential clinical translation, we restricted analysis to biomarkers quantifiable by routine NMR LipoProfile measurement.[12] Whether enhanced multimarker performance can be achieved by inclusion of additional biomarkers will require further study. The populations studied were mostly of White ethnicity and had higher disease risk, so results might not be generalisable to other ethnic and lower-risk groups. Only baseline levels of the metabolic malnutrition–inflammation syndrome biomarkers were used in the analysis, precluding investigation of the effect of dynamic changes of these markers on survival. There are also methodological limitations of the study design and analysis including unmeasured confounding, ignorance of the time-varying nature of exposure and possible feedback between exposure and confounders, and measurement error of the predictive variables and confounders. Finally, the observational nature of our study does not allow causal roles for the MVX biomarkers to be inferred.

Contributors

JDO contributed to study conceptualisation, investigation, methods, project administration, resources, supervision, visualisation, validation, and writing of the original manuscript draft. IS contributed to study conceptualisation, investigation, data curation, formal analysis, methods, computing resources, software, validation, and visualisation. HTM contributed to study conceptualisation, data curation, formal analysis, methodology, computing resources, and validation. JBM contributed to study conceptualisation, study material resources, project administration, and supervision. JTW contributed to methods, supervision, and visualisation. RWM contributed to study conceptualisation, data curation, and resources. WEK contributed to study conceptualisation, methods, project administration, and resources. All authors reviewed and edited the final version of the manuscript. All authors had access to the data and JDO, IS, HTM, and RWM have directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests

JDO is a consultant, stockholder, and former employee of Labcorp. IS is an employee and stockholder of Labcorp. JDO and IS are co-inventors on a patent (US11156621B2) owned by Labcorp relating to multi-variable metabolic vulnerability index evaluations. All other authors declare no competing interests.

Data sharing

Deidentified participant data from the CATHGEN biorepository are available upon reasonable request to the corresponding author with publication under a data sharing agreement. The Intermountain Heart dataset used in this study is not publicly available.

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