Research Square

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Older Adults With Cardiovascular-Kidney-Metabolic Stage 2: Six-Year Risk Stratification Using NT-proBNP and TNFR1

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Research Article

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Abstract

Background

Many older adults without cardiovascular disease meet criteria for CKM stage 2, but their near-term risk may differ substantially. We examined whether NT-proBNP and TNFR1 could distinguish six-year cardiovascular and mortality risk within CKM stage 2.

Methods

We used data from the 2016 Health and Retirement Study Venous Blood Study with follow-up through 2022. Participants were adults aged 50 years or older with measured CKM stage 0–2 and no cardiovascular disease at baseline. The main analysis focused on participants with measured CKM stage 2. NT-proBNP was evaluated using the commonly used clinical cutoff of 125 pg/mL. Among participants with NT-proBNP < 125 pg/mL, TNFR1 was further assessed using threshold analysis, restricted cubic splines, bootstrap validation, decision curve analysis, survey-weighted models, and competing-risk analysis.

Results

Among 6,488 eligible participants, 6,205 (95.6%) were classified as measured CKM stage 2. Within this group, participants with NT-proBNP < 125 pg/mL had lower six-year risk of cardiovascular disease or death than those with NT-proBNP > = 125 pg/mL (15.9% vs 44.0%). Among participants with NT-proBNP < 125 pg/mL, higher TNFR1 identified a subgroup with greater risk (27.5% vs 13.5%; adjusted HR 1.68 (1.37–2.05)). Risk increased stepwise across biomarker-defined groups, and sensitivity analyses showed similar patterns.

Conclusions

In older adults with CKM stage 2, NT-proBNP and TNFR1 identified marked differences in six-year cardiovascular and mortality risk. These biomarkers may help refine risk assessment within CKM stage 2.

1. Introduction

Cardiovascular-kidney-metabolic (CKM) syndrome describes the close clinical connection among metabolic risk, kidney dysfunction, and cardiovascular disease [1–3]. In older adults, obesity, dysglycemia, hypertension, and mild kidney impairment often coexist before clinical cardiovascular disease develops. For this reason, CKM stage 2 may include a large proportion of older adults who are still free of cardiovascular disease but do not necessarily share the same near-term risk.

In the Health and Retirement Study (HRS), this problem was particularly relevant. HRS is a national longitudinal study of US adults aged 50 years or older, with venous blood measures collected in 2016 and follow-up through 2022 [8–10]. In the present analysis, most participants who were free of cardiovascular disease at baseline and had complete measured CKM data fell into CKM stage 2. Therefore, we focused on whether risk could still be separated within this large stage-2 group.

NT-proBNP is a well-established marker of cardiac stress and has been associated with cardiovascular events and mortality in community-based and older-adult populations [11–15]. TNFR1 reflects inflammatory activation and has also been linked to cardiovascular, kidney, and mortality outcomes in aging populations [20–29]. These two biomarkers may therefore capture different aspects of risk in CKM stage 2. In this study, we examined whether NT-proBNP and TNFR1 could distinguish six-year cardiovascular and mortality risk within measured CKM stage 2.

2. Methods

2.1 Study Design and Population

We used data from the Health and Retirement Study (HRS), a nationally representative longitudinal study of US adults aged 50 years or older [8, 9]. The 2016 Venous Blood Study was used as baseline because NT-proBNP and TNFR1 were both measured in that wave [10]. Participants were followed through 2022 for incident cardiovascular disease and death. We included participants aged 50 years or older who had measured CKM stage 0–2, no cardiovascular disease at baseline, available NT-proBNP, and complete main covariate data. The complete-case cohort for CKM stage distribution and NT-proBNP analyses included 6,488 participants, of whom 6,205 were in measured CKM stage 2. TNFR1 analyses were then restricted to stage-2 participants with complete TNFR1, outcome, and model-covariate data.

2.2 Measures

Measured CKM stage was assigned from 2016 interview and venous blood data. The interview instrument was developed and administered by the HRS and was not developed for the present secondary analysis. The 2016 HRS Core interview questionnaires are publicly available from the HRS website [36]. Stage 1 was based on overweight or prediabetic-range glucose, and stage 2 was based on diabetes, hypertension, dyslipidemia, or creatinine-based chronic kidney disease. Participants with baseline self-reported heart disease or stroke were considered to have clinical cardiovascular disease and were excluded; stage 3 was not assigned because formal subclinical cardiovascular imaging and risk-equation inputs were not fully available in HRS. The main biomarker analysis was conducted within measured CKM stage 2. NT-proBNP was evaluated using the commonly used 125 pg/mL cutoff. Among participants with NT-proBNP < 125 pg/mL, TNFR1 was then examined to assess whether risk could be further separated. The primary outcome was the six-year composite of incident cardiovascular disease or death. Secondary outcomes were incident cardiovascular disease and death separately. Incident cardiovascular disease included newly reported heart disease or stroke.

2.3 Statistical Analysis

We first described baseline characteristics in the overall cohort and across biomarker groups within measured CKM stage 2. Associations of NT-proBNP and TNFR1 with six-year outcomes were examined using multivariable Cox models adjusted for age, sex, education, race/ethnicity, smoking, drinking, body mass index, diabetes, total cholesterol, high-density lipoprotein cholesterol, and creatinine-based estimated glomerular filtration rate. TNFR1 models within the NT-proBNP < 125 pg/mL subgroup additionally retained continuous log NT-proBNP. Candidate TNFR1 thresholds from the 60th to 90th percentiles were scanned, and the threshold with the lowest adjusted Cox Akaike information criterion for cardiovascular disease or death was selected. Threshold stability was assessed using 300 bootstrap samples. Absolute risks were compared across biomarker-defined groups. Incremental clinical value was evaluated using reclassification analyses, decision curve analysis, survey-weighted models, proportional-hazards diagnostics, and competing-risk analysis for incident cardiovascular disease [30–35].

3. Results

Among 6,488 participants with measured CKM stage 0–2 and no cardiovascular disease at baseline, 6,205 (95.6%) were classified as measured CKM stage 2 (Table 1). This concentration in stage 2 supported focusing the main analysis on risk differences within this group. For the TNFR1 analysis, 6,094 stage-2 participants had complete TNFR1, outcome, and model-covariate data; 4,055 of them had NT-proBNP < 125 pg/mL and formed the threshold-analysis subgroup.

Table 1
Analytic cohort and biomarker sample.

Step	N	Events
Complete-case measured CKM stage 0–2 cohort	6488	1618
Measured CKM stage 2	6205	1570
Stage 2 complete-case for TNFR1 analysis	6094	1545
Stage 2 with NT-proBNP < 125 for TNFR1 threshold analysis	4055	645
Stage 2 with NT-proBNP < 125 and TNFR1 above threshold	690	190

Note. The first two rows describe the complete-case CKM and NT-proBNP cohort; subsequent rows describe the TNFR1 complete-case analysis. Events refer to cardiovascular disease or death over six years. CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TNFR1, tumor necrosis factor receptor 1.

Within measured CKM stage 2, NT-proBNP separated participants into groups with markedly different six-year risks (Fig. 1; Table 2). Participants with NT-proBNP < 125 pg/mL had a lower risk of cardiovascular disease or death than those with NT-proBNP > = 125 pg/mL (15.9% vs 44.0%). However, a

substantial number of events still occurred in the lower NT-proBNP group, supporting further assessment within this subgroup.

Among CKM stage-2 participants with NT-proBNP < 125 pg/mL, TNFR1 further separated risk (Fig. 2; Table 2). Using a TNFR1 cutoff of 1906.7 pg/mL, participants with higher TNFR1 had about twice the six-year risk of cardiovascular disease or death compared with those with lower TNFR1 (27.5% vs 13.5%). This association remained significant after multivariable adjustment (HR 1.68 (1.37–2.05)).

Table 2
Six-year risk across biomarker groups.

Outcome	Risk group	N/events	Observed 6-year risk	Adjusted HR vs low group
Incident cardiovascular disease	Low residual risk	3365/297	8.9% (8.0-9.9)	Reference
Incident cardiovascular disease	Inflammatory residual risk	690/99	14.9% (12.1–17.6)	1.39 (1.09–1.77)
Incident cardiovascular disease	Cardiac stress risk	2039/454	24.0% (22.0-25.9)	2.57 (2.17–3.04)
Death	Low residual risk	3365/170	5.1% (4.3–5.8)	Reference
Death	Inflammatory residual risk	690/98	14.2% (11.6–16.8)	1.75 (1.35–2.27)
Death	Cardiac stress risk	2039/525	25.7% (23.8–27.6)	2.97 (2.44–3.60)
Cardiovascular disease or death	Low residual risk	3365/455	13.5% (12.4–14.7)	Reference
Cardiovascular disease or death	Inflammatory residual risk	690/190	27.5% (24.1–30.8)	1.56 (1.31–1.87)
Cardiovascular disease or death	Cardiac stress risk	2039/900	44.1% (41.9–46.3)	2.78 (2.44–3.16)

Note. Observed risks are six-year risks with 95% CIs. Hazard ratios compare each group with the low-risk group. CKM, cardiovascular-kidney-metabolic; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TNFR1, tumor necrosis factor receptor 1.

When NT-proBNP and TNFR1 were considered together, six-year risk increased stepwise across biomarker-defined groups (Fig. 1; Table 2). The risk of cardiovascular disease or death was 13.5% among participants with NT-proBNP < 125 pg/mL and lower TNFR1, 27.5% among those with NT-proBNP < 125 pg/mL and higher TNFR1, and 44.1% among those with NT-proBNP > = 125 pg/mL. A similar pattern was observed for incident cardiovascular disease and death when analyzed separately.

Among participants with NT-proBNP < 125 pg/mL, TNFR1 provided additional risk separation for cardiovascular disease or death beyond the clinical model (Fig. 3). When TNFR1 was entered as a binary group using the 1906.7 pg/mL cutoff, the C-index increased from 0.663 to 0.674 and AIC decreased by 22.1. Decision curve analysis showed a small increase in net benefit. The additional separation was more evident for death and the composite outcome than for incident cardiovascular disease alone.

Sensitivity analyses supported the main findings (Fig. 4; Additional file 1: Supplementary Tables 1–3). In bootstrap resampling, the TNFR1 cutoff showed limited variation, with most estimates close to 1906.7 pg/mL. Survey-weighted models and competing-risk analyses produced similar results. Restricted cubic spline analyses also showed higher risk of cardiovascular disease or death at higher TNFR1 levels among participants with NT-proBNP < 125 pg/mL.

4. Discussion

This study showed substantial variation in six-year risk among older adults who were classified as CKM stage 2 and had no cardiovascular disease at baseline. NT-proBNP > = 125 pg/mL identified participants with markedly higher risk of cardiovascular disease or death. Among participants with NT-proBNP < 125 pg/mL, higher TNFR1 further identified a subgroup with nearly doubled absolute risk. These findings suggest that NT-proBNP and TNFR1 can help refine risk assessment within measured CKM stage 2.

Previous studies have shown that NT-proBNP predicts cardiovascular events and mortality in community-based and older-adult populations. Other studies have linked TNFR1 to cardiovascular, kidney, and mortality outcomes. Our study extends this evidence by evaluating both biomarkers within the CKM staging context. Rather than focusing only on prediction in the overall cohort, we focused on the large group classified as CKM stage 2 and examined whether these biomarkers could separate risk within that stage [4–7, 11–29].

In clinical practice, many older adults with obesity, metabolic abnormalities, or mild kidney impairment would be classified as CKM stage 2. Our results indicate that this classification does not represent a uniform level of near-term risk. A lower NT-proBNP level identified a lower-risk group, but TNFR1 further separated a subgroup whose risk was no longer low. This finding may help avoid treating all lower-NT-proBNP stage-2 individuals as having similarly low risk.

NT-proBNP and TNFR1 may reflect different biological processes. NT-proBNP mainly reflects cardiac wall stress and subclinical cardiac dysfunction, which may explain its strong association with cardiovascular events and death. TNFR1 is related to inflammatory and systemic stress pathways that are also involved in vascular injury, kidney dysfunction, frailty, and mortality. Therefore, TNFR1 may capture part of the risk that is not reflected by NT-proBNP alone, especially in older adults whose risk may arise from multiple organ systems.

A strength of this study is the use of a national aging cohort with venous blood biomarkers and follow-up for both cardiovascular events and death. We also examined the findings using several complementary

approaches, including absolute risk estimates, adjusted models, decision curve analysis, survey weighting, and competing-risk analysis. The study has limitations. The TNFR1 cutoff was derived from HRS and requires validation in an independent cohort. Incident cardiovascular disease was based on self-reported physician diagnosis, and residual confounding remains possible.

5. Conclusion

Among older adults with measured CKM stage 2 and no cardiovascular disease at baseline, six-year risk varied substantially. NT-proBNP identified a high-risk group, and TNFR1 further separated risk among participants with NT-proBNP < 125 pg/mL. These findings suggest that complementary blood biomarkers may help identify clinically meaningful risk differences within CKM stage 2.

Declarations

Availability of data and materials: HRS public data are available to registered users through the HRS website (https://hrs.isr.umich.edu/data-products/access-to-public-data). Sensitive and restricted files require separate HRS approval. Analysis code used to generate the present tables and figures is available from the corresponding author on reasonable request.

Ethics approval and consent to participate: The parent Health and Retirement Study was approved by the University of Michigan Health Sciences and Behavioral Sciences Institutional Review Board, University of Michigan (protocol HUM00061128), and all participants provided informed consent. All methods were carried out in accordance with relevant guidelines and regulations, including the Declaration of Helsinki. The present study was a secondary analysis of de-identified HRS data.

Clinical trial number: not applicable.

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Sirui Sun contributed to conceptualization, data curation, formal analysis, visualization, and drafting of the manuscript. Jie Zhang contributed to supervision, methodology, interpretation, and critical revision of the manuscript. Both authors approved the final manuscript.

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Declaration of Generative AI and AI-Assisted Technologies in the Manuscript Preparation Process: During the preparation of this work, the authors used OpenAI ChatGPT/Codex to assist with language editing, formatting, citation checking, and scripted document generation. After using this tool,

the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Figures

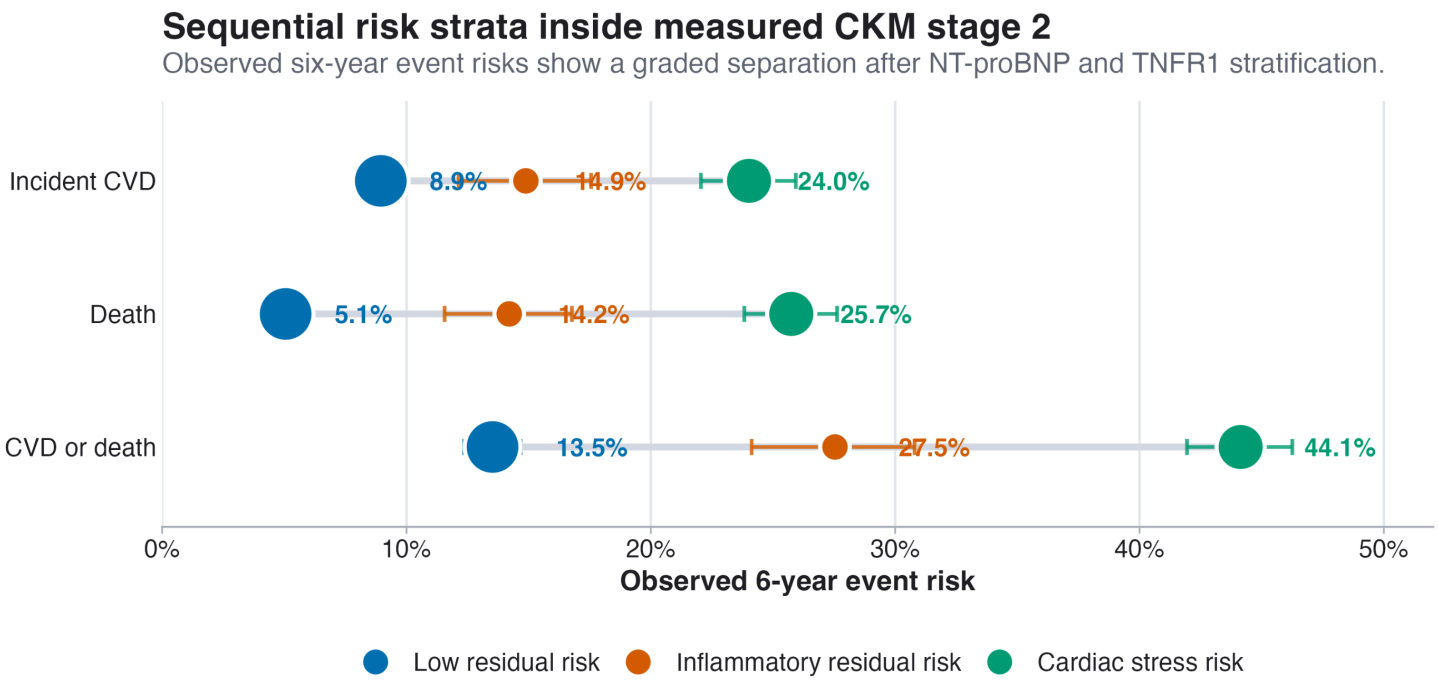


Figure 1

Biomarker-defined risk groups in CKM stage 2.Observed six-year risks are shown as a risk ladder for incident CVD, death, and CVD or death; point size reflects subgroup size and horizontal bars show 95% CIs.

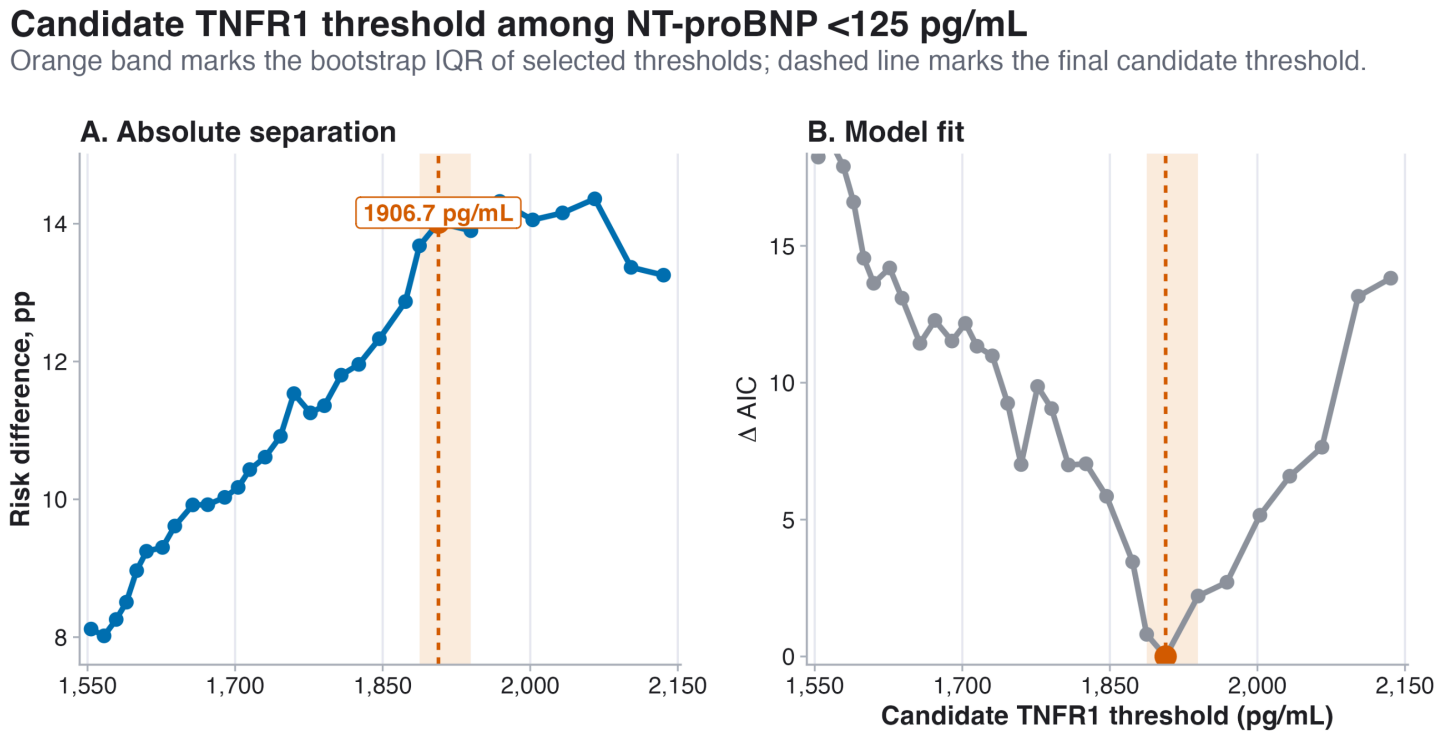


Figure 2

TNFR1 threshold scan within the NT-proBNP <125 subgroup. The selected threshold minimizes adjusted Cox AIC for CVD or death; the orange band shows the bootstrap IQR of selected thresholds.

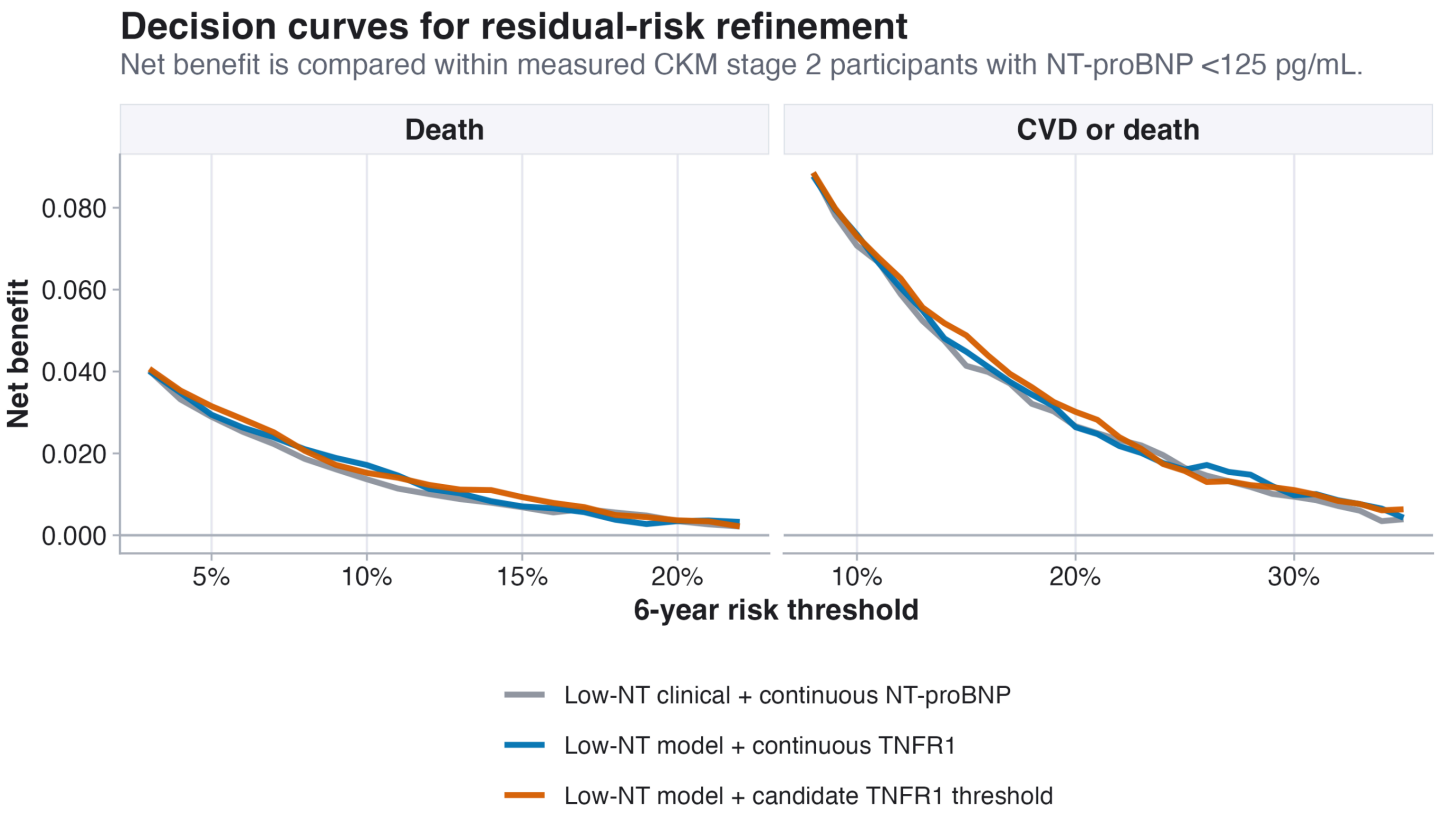


Figure 3

Decision curves for adding TNFR1. Net benefit is compared with the low-NT clinical model that retains continuous NT-proBNP.

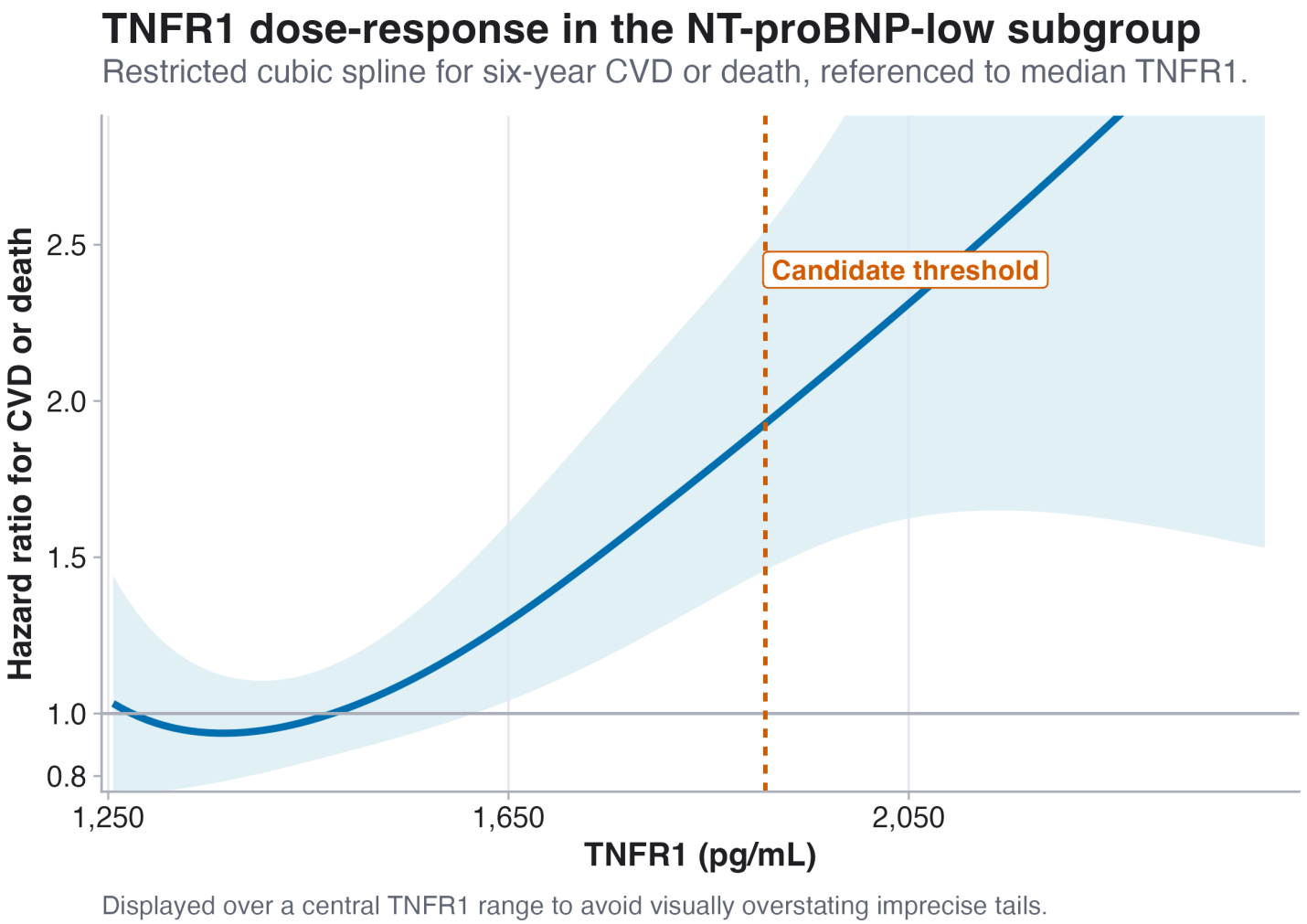


Figure 4

TNFR1 dose-response among NT-proBNP <125 participants.Restricted cubic spline HRs for CVD or death are relative to the median TNFR1 level and displayed over a central TNFR1 range.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfileslegend.docx
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