



# Associations between midlife metabolic syndrome clusters, their trajectories, and incident dementia: The ARIC Neurocognitive Study

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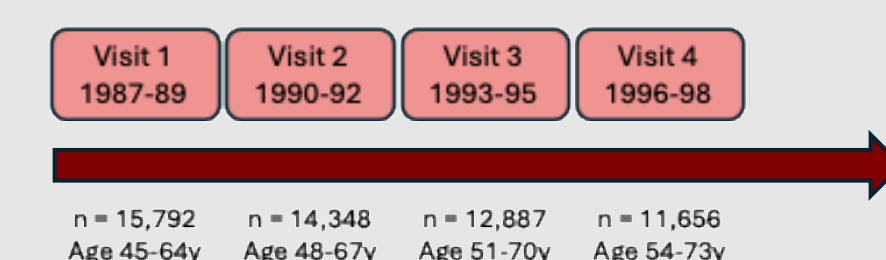
## BACKGROUND

Metabolic syndrome (MetS) is associated with an increased risk of dementia. However, the dementia risk associated with different numbers and patterns of MetS components, and their changes over time, is unclear.

## STUDY AIMS

- 1: Evaluate the association between MetS and incident dementia.
- 2: Investigate the relationship between different clusters of MetS components and incident dementia.
- 3: Explore the association between different trajectories in MetS cluster membership and incident dementia.

## METHODS



**EXPOSURE: MetS** MetS was defined as the presence of  $\geq 3$  of the following: 1) **high waist circumference** (male:  $\geq 102$  cm; female:  $\geq 88$  cm); 2) **high blood pressure** ( $\geq 130$  mmHg systolic,  $\geq 85$  mmHg diastolic, or medication use); 3) **hyperglycemia** (FPG  $\geq 100$  mg/dl or medication use); 4) **high triglycerides** ( $\geq 150$  mg/dL); and 5) **low HDL** (male:  $< 40$  mg/dL; female:  $< 50$  mg/dL).

**OUTCOME: Dementia** Incident dementia was ascertained from in-person adjudication at clinical examinations, telephone data from participants/informants, and hospital/death records (until end of 2022)

### STATISTICAL ANALYSIS

In Aim 1, Cox regression models were used to estimate the association between MetS status (at ARIC Visit 1) and incident dementia.

In Aims 2 and 3, clusters of MetS components were identified using hierarchical clustering based on principal components (HCPC) with k-means consolidation. MetS components with an observed/expected ratio  $\geq 1.5$  and marginal proportion  $\geq 25\%$  within a given cluster were considered defining features of that cluster. Cox regression models were used to estimate the association of MetS clusters (at ARIC Visit 1) and cluster trajectories (from ARIC Visit 1 to Visit 4) with incident dementia.

In all analyses, Model 1 included age, sex, race/center, and education and Model 2 additionally included cigarette smoking, alcohol consumption, physical activity, and APOE  $\epsilon 4$  genotype.

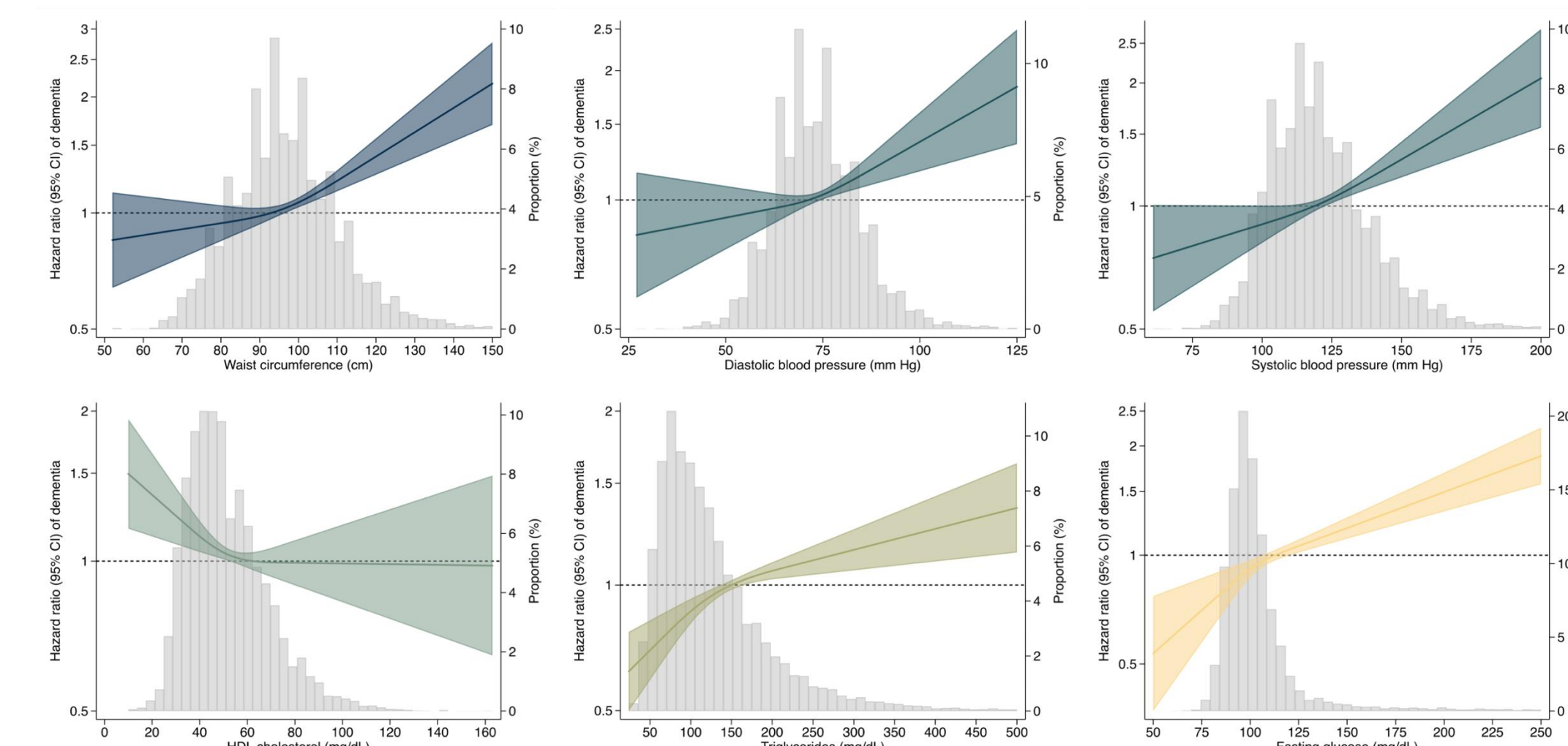
## RESULTS: Association of MetS and its components with dementia

MetS at Visit 1 was associated with significantly increased risk of dementia (Table 1). Furthermore, as continuous variables, all MetS measures were individually related to dementia risk (Figure 1).

Table 1. Association between MetS and dementia

|              | n     | Model 1                  | Model 2                  |
|--------------|-------|--------------------------|--------------------------|
|              |       | HR (95% CI)              | HR (95% CI)              |
| MetS-free    | 8,931 | Reference                | Reference                |
| MetS         | 5,795 | <b>1.41 (1.32, 1.51)</b> | <b>1.46 (1.32, 1.62)</b> |
| 0 components | 2,047 | Reference                | Reference                |
| 1 component  | 3,459 | <b>1.16 (1.03, 1.30)</b> | 1.18 (0.96, 1.46)        |
| 2 components | 3,425 | <b>1.22 (1.08, 1.37)</b> | <b>1.28 (1.05, 1.57)</b> |
| 3 components | 3,008 | <b>1.51 (1.35, 1.70)</b> | <b>1.64 (1.34, 2.00)</b> |
| 4 components | 1,940 | <b>1.63 (1.43, 1.85)</b> | <b>1.75 (1.41, 2.17)</b> |
| 5 components | 847   | <b>2.07 (1.75, 2.45)</b> | <b>2.26 (1.74, 2.94)</b> |

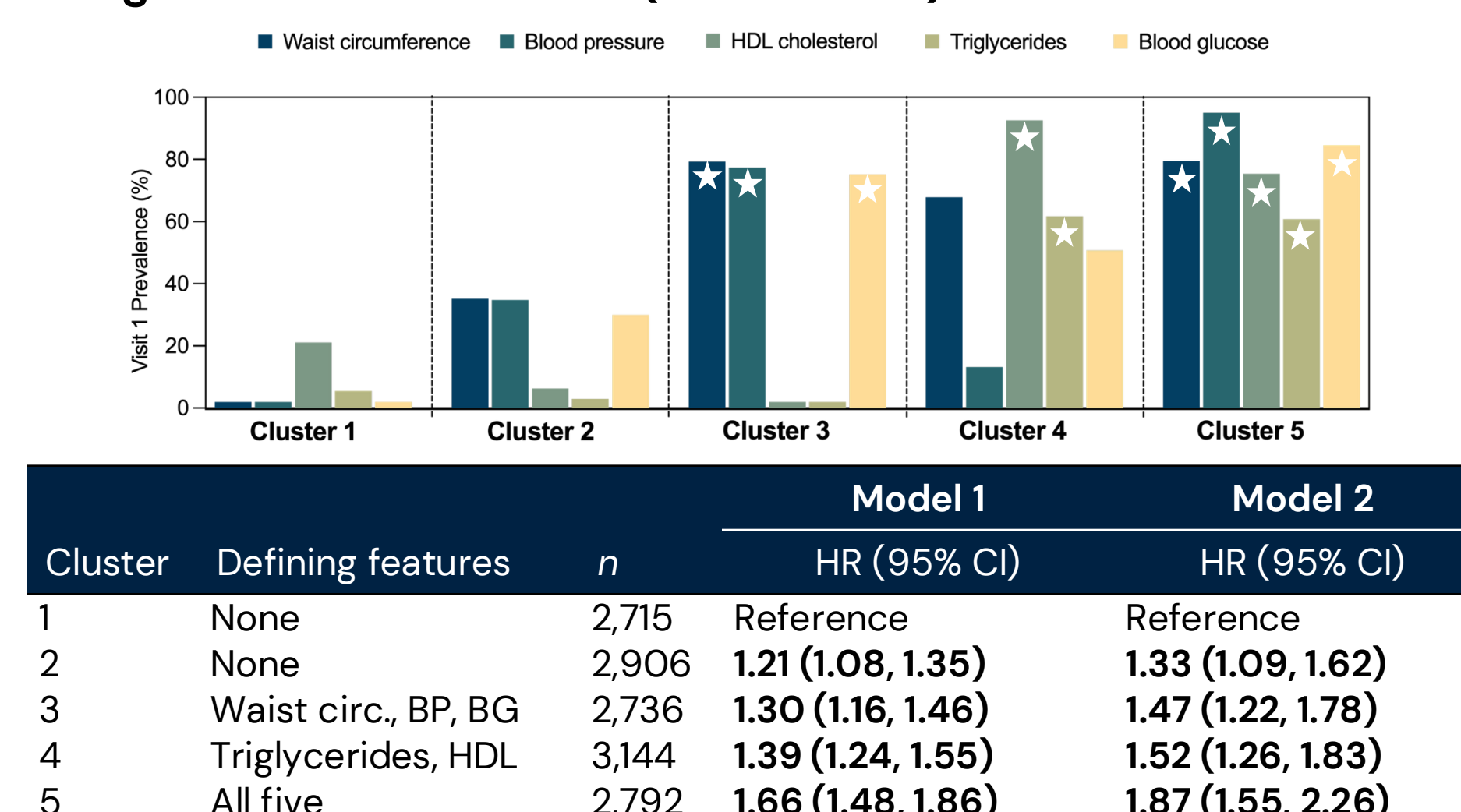
Figure 1. Continuous MetS measures in relation to dementia risk



## RESULTS: Association of MetS clusters and their trajectories with dementia

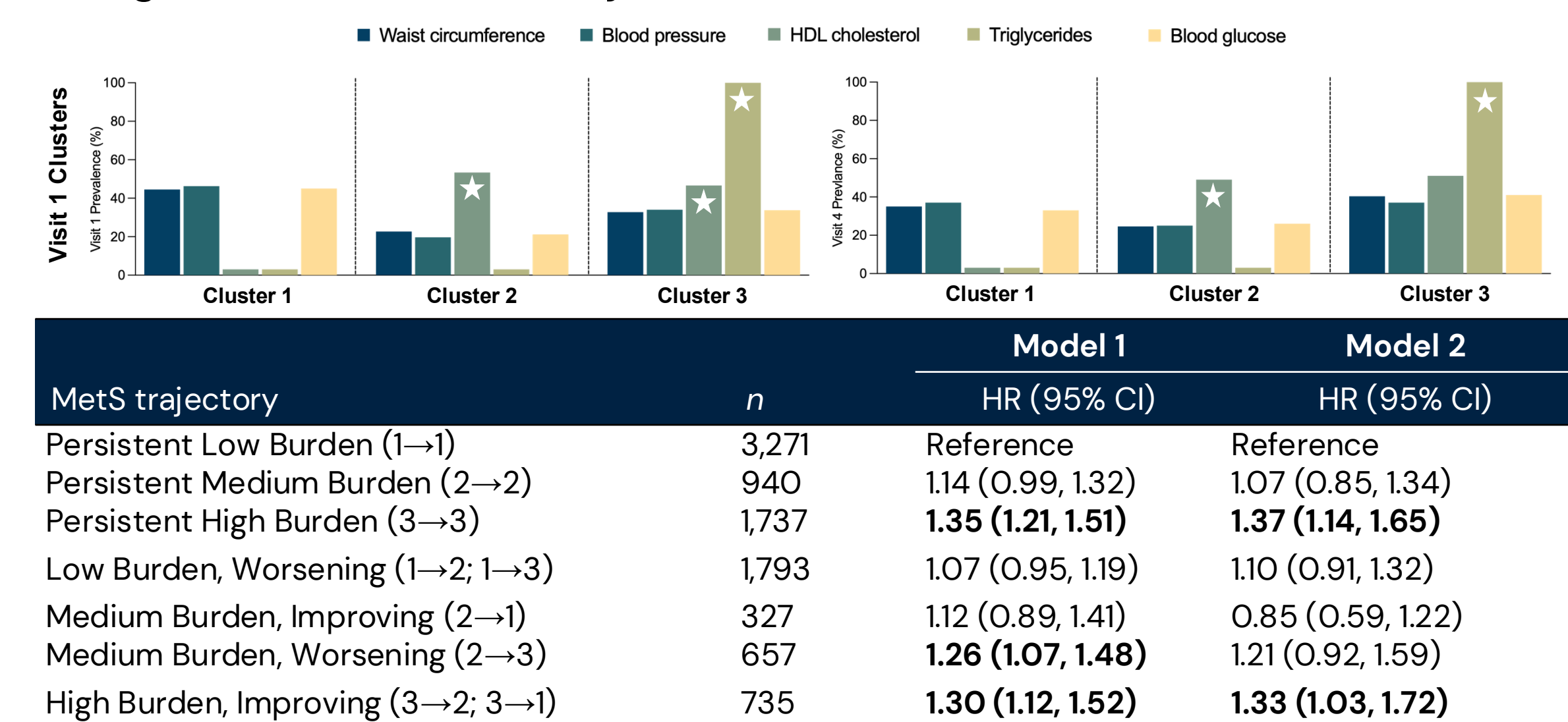
Cluster analysis identified five metabolically distinct clusters at Visit 1; dementia risk increasing monotonically across clusters (Figure 2). In trajectory analysis, clusters were re-derived at Visits 1 and 4 among participants with available MetS data at both timepoints. Both persistent membership in Cluster 3 and transition from Cluster 3 to Cluster 1 or 2 were associated with elevated dementia risk, compared to membership in Cluster 1 (Figure 3).

Figure 2. MetS clusters (ARIC Visit 1) and dementia risk



| Cluster | Defining features   | n     | Model 1                  | Model 2                  |
|---------|---------------------|-------|--------------------------|--------------------------|
|         |                     |       | HR (95% CI)              | HR (95% CI)              |
| 1       | None                | 2,715 | Reference                | Reference                |
| 2       | None                | 2,906 | <b>1.21 (1.08, 1.35)</b> | <b>1.33 (1.09, 1.62)</b> |
| 3       | Waist circ., BP, BG | 2,736 | <b>1.30 (1.16, 1.46)</b> | <b>1.47 (1.22, 1.78)</b> |
| 4       | Triglycerides, HDL  | 3,144 | <b>1.39 (1.24, 1.55)</b> | <b>1.52 (1.26, 1.83)</b> |
| 5       | All five            | 2,792 | <b>1.66 (1.48, 1.86)</b> | <b>1.87 (1.55, 2.26)</b> |

Figure 3. MetS cluster trajectories (ARIC Visit 1 to 4) and dementia risk



| MetS trajectory                   | n     | Model 1                  | Model 2                  |
|-----------------------------------|-------|--------------------------|--------------------------|
|                                   |       | HR (95% CI)              | HR (95% CI)              |
| Persistent Low Burden (1→1)       | 3,271 | Reference                | Reference                |
| Persistent Medium Burden (2→2)    | 940   | 1.14 (0.99, 1.32)        | 1.07 (0.85, 1.34)        |
| Persistent High Burden (3→3)      | 1,737 | <b>1.35 (1.21, 1.51)</b> | <b>1.37 (1.14, 1.65)</b> |
| Low Burden, Worsening (1→2; 1→3)  | 1,793 | 1.07 (0.95, 1.19)        | 1.10 (0.91, 1.32)        |
| Medium Burden, Improving (2→1)    | 327   | 1.12 (0.89, 1.41)        | 0.85 (0.59, 1.22)        |
| Medium Burden, Worsening (2→3)    | 657   | <b>1.26 (1.07, 1.48)</b> | 1.21 (0.92, 1.59)        |
| High Burden, Improving (3→2; 3→1) | 735   | <b>1.30 (1.12, 1.52)</b> | <b>1.33 (1.03, 1.72)</b> |

## TAKE HOME MESSAGE

Dementia risk may be informed not only by the number of MetS components present but also their specific combinations, as well as their persistence over midlife.



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