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RESEARCH ARTICLE

Association of change in cardiovascular risk factors with incident dementia

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Abstract

Introduction: We evaluated whether better cardiovascular health at midlife and improvement of cardiovascular health within midlife were associated with dementia risk.

Methods: Two longitudinal population-based studies were used: Atherosclerosis Risk in Communities (ARIC) (n = 11,460/visits at ages 54 and 60), and Age, Gene/Environment Susceptibility (AGES)-Reykjavik (n = 3907/visit at age 51). A cardiovascular health score (range 0–12/0–14, depending on diet availability) including six/seven items was calculated at each visit, with weight assigned to each item as poor (0), intermediate (1), or ideal (2). Cardiovascular health was defined as low (score 0–4/0–5), intermediate (5–7/6–9), or high (8–12/10–14). Incident dementia was ascertained through linkage to health records and with neuropsychological examinations.

Results: Midlife high compared to low cardiovascular health (hazard ratios [HRs]: for ARIC: 0.60 [95% confidence interval: 0.52, 0.69]); for AGES-Reykjavik: 0.83 [0.66,

0.99] and improvement of cardiovascular health score within midlife (HR per one-point increase: ARIC: 0.94 [0.92, 0.96]) were associated with lower dementia risk.
Discussion: Better cardiovascular health at midlife and improvement of cardiovascular health within midlife are associated with lower dementia risk.

KEYWORDS
cardiovascular health, dementia, life course, longitudinal, primordial prevention

Highlights

- Cardiovascular health and dementia were studied in two large cohort studies.
- Better cardiovascular health at midlife relates to lower dementia risk.
- Improvement of cardiovascular health within midlife relates to lower dementia risk.
- Promotion of cardiovascular health at midlife can help to reduce dementia risk.

1 | BACKGROUND

Dementia is a devastating medical condition and efforts to treat this clinical entity have largely been unsatisfactory. Early prevention of cognitive decline before manifestations of dementia symptoms is therefore critical.[1,2] Given the multifactorial nature of dementia, interventions targeting several risk factors simultaneously and across the life course may be required for optimal preventive outcomes.[1,2] Vascular risk factors are increasingly recognized as important contributors to the development of dementia and, thus, as potential targets for early preventive therapies.[1,3]

To date, much of the evidence is on cardiovascular risk factors assessed during a single examination only, either in midlife or late-life. Furthermore, most studies focused on primary or secondary prevention. Yet, prevention of risk factors before they emerge (primordial prevention) may be most efficient to prevent or delay the onset of dementia. For primordial prevention of cardiovascular risk factors, the American Heart Association (AHA) developed a simple 7-item cardiovascular health (CVH) tool consisting of four behavioral metrics (nonsmoking, and ideal levels of body mass index, physical activity, and dietary habits) and three biological metrics (ideal levels of blood pressure, blood glucose, and total cholesterol).[4] However, whether this construct may be used as a tool for the prevention of dementia is still debated.[3] Some studies have shown that adherence to the CVH recommendations at midlife[5,6] or at late-life[7] are associated with lower risk of dementia, although data are not consistent across studies.[8–10] A reason posed for the inconsistency is that results of studies that evaluated CVH at late-life and risk of dementia[7,8] are difficult to interpret, because these results may be affected by various biases, for example, bias due to reverse causality and attrition bias. Also, due to long preclinical phase of dementia, importance of studying midlife risk factors has been emphasized.[11,12] Several studies have examined trajectories of individual risk factors, including hypertension, obesity, and dyslipidemia in the period preceding dementia diagnosis and have shown an age-dependent pattern in the association of these risk factors and risk of dementia.[13–15] However, whether change in CVH within midlife relates to subsequent risk of dementia is unknown. If improvement of cardiovascular health is associated with lower dementia risk, this would provide strong support for public health policies to focus on primordial prevention and improve CVH to prevent dementia.

Using serial examinations of two population-based cohorts from different time periods, the Atherosclerosis Risk in Communities (ARIC) study, and the Age, Gene/Environment Susceptibility (AGES)-Reykjavik study, we sought to evaluate whether higher CVH at midlife and improvement of CVH within midlife were associated with lower risk of dementia. In a secondary analysis, we sought to evaluate whether higher CVH at late-life and improvement of CVH from midlife to late-life were associated with lower risk of dementia.

2 | METHODS

2.1 | Study populations

ARIC is an ongoing population-based study started in 1987 to 1989 (visit 1) and included 15,792 individuals aged 45 to 64 years from four US communities (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and suburban Minneapolis, Minnesota).[16] Participants were evaluated in person every 3 years, including visit 2 (1990–1992), visit 3 (1993–1995), and visit 4 (1996–1998). Fifteen years later, participants were invited back for visit 5 (2011–2013). Participants returned for visit 6 (2016–2017) and visit 7 (2018–2019). To evaluate CVH at midlife and change within midlife, we included 11,460 participants with information on dementia status and CVH at both visits 1 and 3, when participants had a mean age of 54 and 60, respectively (Figure 1).

The AGES-Reykjavik study was launched in 1967 and included 19,390 randomly selected subjects born between 1907 and 1935 living in Reykjavik, Iceland. Participants were re-invited between 1967 and 1996 for follow-up examinations.[17] The AGES-Reykjavik study (AGES-I) was done between 2002 and 2006 and included 5764 subjects aged 66 to 98 who were randomly selected from the Reykjavik cohort who

were alive (response rate approximately 70%). A follow-up examination (AGES-II) was done from 2007 to 2011.[18] For this analysis, we included 3907 participants with information on dementia status and CVH at midlife (Figure 2). To evaluate CVH at midlife in the Reykjavik study, we used data from the closest measurement to 50 years.[18]

Both studies were approved by institutional review boards and written informed consent was signed by all participants.

For the secondary analysis investigating CVH at late-life and change in CVH from midlife to late-life, we included 5011 participants from ARIC who had available information on dementia status and CVH at both visits 1 and 5 (Figure 1). At visit 5, participants had a mean age of 75. For AGES-Reykjavik, late-life CVH data were obtained from the AGES-I examination when participants had a mean age of 76 (Figure 2).

2.2 | CVH metrics

The AHA criteria were used to define the CVH metrics (Table 1). Dietary habits were available at ARIC midlife visits 1 and 3 but not at the AGES-Reykjavik midlife visit; therefore, we used six metrics to compile a CVH for the AGES-Reykjavik midlife visit, as done previously.[19,20] A continuous CVH score was calculated assigning a score of 0 for poor metrics, 1 for intermediate metrics, and 2 for ideal metrics. We used a 14-point CVH score using seven items at ARIC visits 1 and 3, and a 12-point CVH score using six items (not including dietary habits) at the AGES-Reykjavik midlife visit. For the 14-point score, we categorized the score as low (scores of 0–5), moderate (6–9), or high (10–14). The 12-point score was categorized as low (scores of 0–4), moderate (5–7), or high (8–12), as done in previous studies.[8]

For change in CVH categories within midlife, the following sefen categories were retained in the analysis to include groups that were sufficiently large and based on previous literature:[8,21] (1) constantly low, (2) low-to-moderate/high, (3) moderate-to-low,; (4) constantly moderate, (5) moderate-to-high, (6) high-to-low/moderate, and (7) constantly high CVH. In addition, change in the continuous CVH score within midlife was evaluated.

2.3 | Dementia incidence

In ARIC, dementia was assessed using a validated, standardized battery of cognitive measures and supplemented by dementia surveillance between visits, by hospital discharge, or death certificate.[22–26] In addition, from 2012, the Telephone Interview for Cognitive Status was used for those who did not attend visit 5 as well as twice-yearly the six-item screener followed by a proxy assessment (when warranted from 2012 and later). The information on dementia was reviewed by a neurologist or geriatrician and a neuropsychologist.[22] The dementia onset was the earliest date determined by dementia surveillance, hospital discharge, or death certificate code. In AGES-Reykjavik, dementia case ascertainment was done via two methods.[27–29] All participants were continuously tracked for dementia diagnosis (any type) through vital statistics and hospital records, and the nursing and home-based Resident Assessment Instrument. In addition, at AGES-I and AGES-II, a three-step procedure was used to identify participants with dementia. The Mini-Mental State Examination and the Digit Symbol Substitution Test were administered to all participants. Screen positives were administered a diagnostic battery of neuropsychological tests, and among them, screen positives were examined by a neurologist and a proxy interview was administered. A consensus diagnosis was made by a panel of experts including a geriatrician, neurologist, neuroradiologist, and neuropsychologist. Follow-up time for incident dementia extended until the first dementia diagnosis, death, loss to follow-up, or December 2019 (ARIC) or December 2015 (AGES-Reykjavik).

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors searched PubMed and Google Scholar and reference lists of relevant articles. Some studies have shown that adherence to the cardiovascular health recommendations at midlife or at late-life are associated with lower risk of dementia, although data have been inconsistent across studies. Also, whether maintaining improving cardiovascular health through life relates to risk of dementia is unknown.
2. **Interpretation**: The findings show that higher cardiovascular health at midlife and improvement in cardiovascular health within midlife are associated with lower risk of dementia. This may have important public health implications highlighting the need for promotion and maintaining ideal cardiovascular health at midlife to reduce risk of dementia.
3. **Future Directions**: Future work should assess whether change in cardiovascular health before midlife (i.e., young adulthood or earlier) is also associated with lower risk of dementia. Dementia has a long preclinical phase and, thus, information on change in cardiovascular health through the lifespan from early in life onward has important public health implications.

2.4 | Statistical analysis

2.4.1 | Primary analysis

We used the Kaplan–Meier method to estimate cumulative dementia incidence curves associated with change in CVH within midlife. The hazard ratios (HRs) with corresponding 95% confidence intervals (95% CIs) of incident dementia were computed in Cox models to evaluate the associations of categories of CVH with the low CVH group as the reference. The HR per 1-point higher continuous CVH score was also estimated. Cox models were used to evaluate the associations of change in categories of CVH and per 1-point increase in the continuous CVH score within midlife. For the analysis with change in categories of CVH, the consistently low CVH group served as the reference.

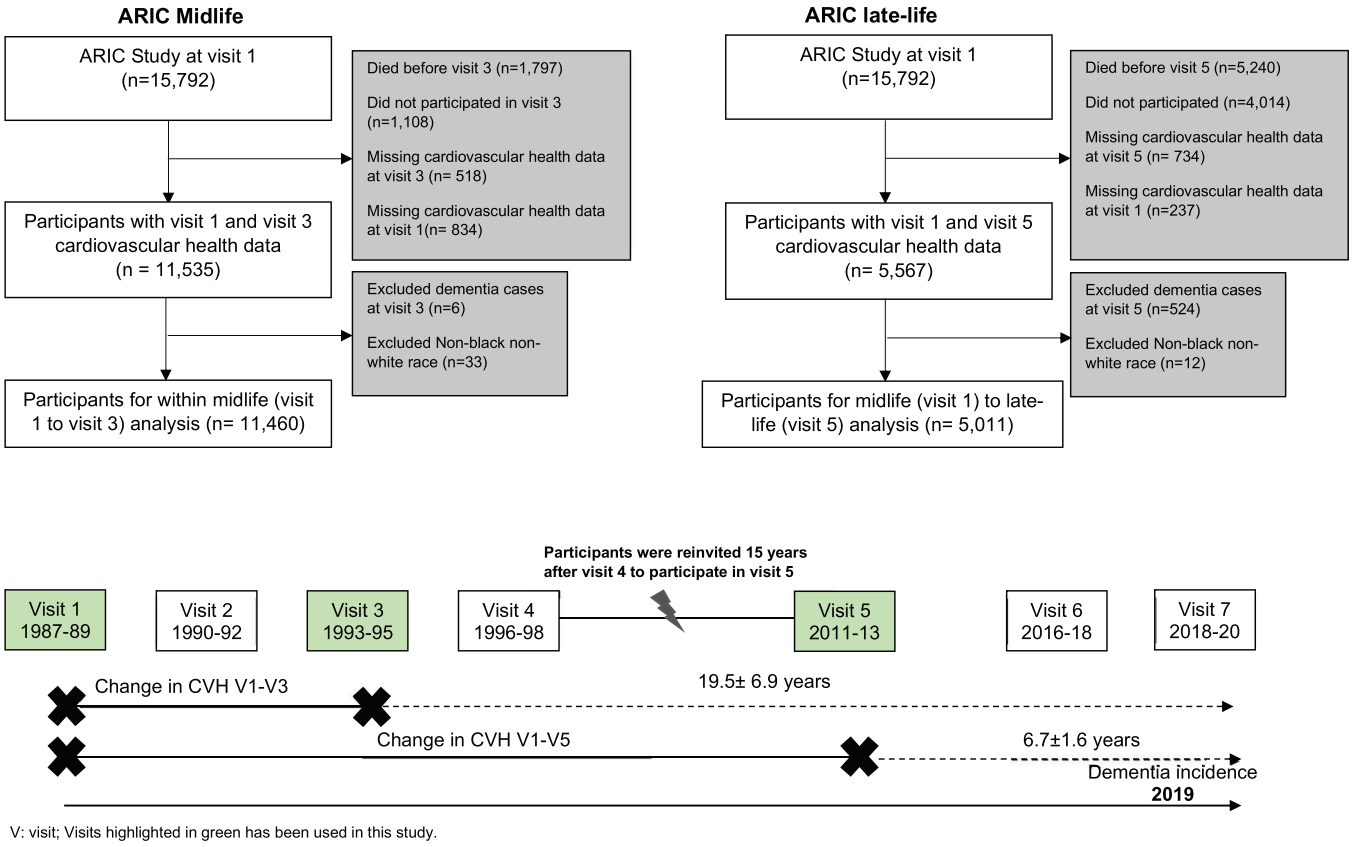

FIGURE 1 Atherosclerosis Risk in Communities (ARIC): study population and design. CVH, cardiovascular health

All models used age as the time scale with left truncation at the time of study entry, and were adjusted for sex and education. Analyses using change in CVH as independent variable were additionally adjusted for the corresponding baseline CVH score. For ARIC, analyses were additionally adjusted for race plus field center (to take into account differences per center). The proportional hazard assumptions were not violated, as assessed by visual inspection of the survival curves and assessing Schoenfeld residuals.

2.4.2 | Secondary analysis

We explored the association between CVH at late-life and change from midlife to late-life with incident dementia in ARIC and AGES-Reykjavik with similar models as used for the analyses on CVH at midlife and change of CVH within midlife.

2.4.3 | Sensitivity analyses

We evaluated the association between individual items of CVH at midlife with dementia risk, with the poor category as reference. To explore residual confounding due to stroke and other cardiovascular disease and to focus on primordial prevention, we repeated the main analysis after exclusion of participants with history of cardiovascular disease at baseline. Furthermore, to evaluate whether associations differed according to the overall genetic risk for dementia, we checked whether the association of change in CVH within midlife and dementia incidence is different in those who have the apolipoprotein E (*APOE*) ε4 variant compared to those without by checking multiplicative interaction between change in CVH within midlife and *APOE* ε4 carriership. To explore whether any of the individual CVH score metrics drives the association, we excluded metrics one by one and re-created the score without the removed item and assessed the association of the new score with incident dementia. To investigate whether death before dementia has influenced the findings, we repeated the analysis using mortality as the outcome.

All analyses were done using R software, version 3.6.0.

3 | RESULTS

The characteristics of the study populations are given in Table 2. In ARIC, 31% of participants had high CVH at midlife and 35% improved their CVH category within midlife. In AGES-Reykjavik, 31% had high CVH at midlife. The level of the individual metrics at each visit in both studies are given in Table S1 in supporting information. Individuals excluded from the analysis compared to those included were older and had a less favorable cardiovascular risk profile (Table S2 in supporting information).

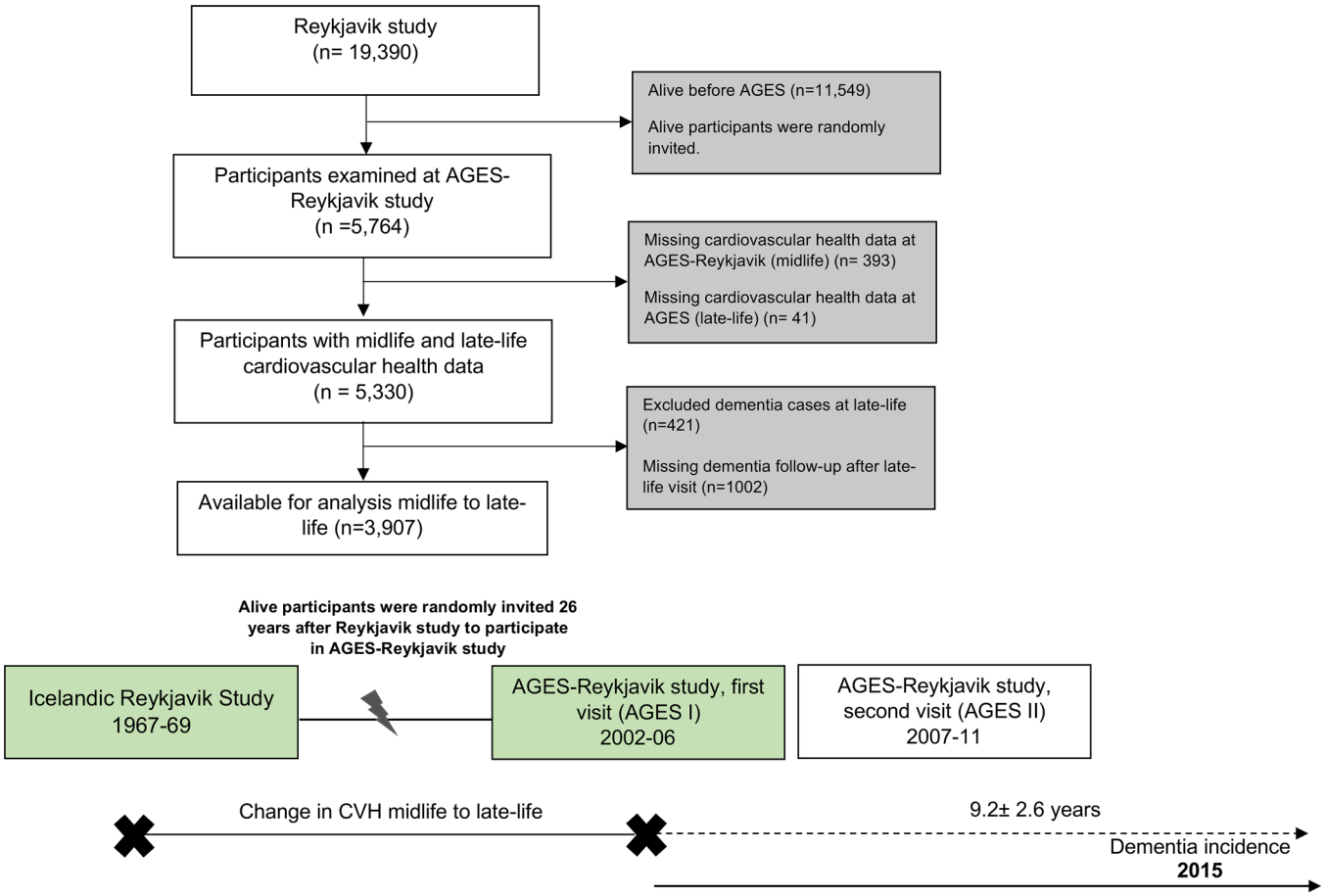

FIGURE 2 Age, Gene/Environment Susceptibility (AGES)-Reykjavik: study population and design. CVH, cardiovascular health

3.1 | CVH at midlife

In ARIC, over a median follow-up of 22.3 years (interquartile range 15.7–24.8) starting from visit 3, 2264 (19.8%) participants were diagnosed with dementia. Participants had a mean age of 54 (standard deviation [SD]: 6, min: 44/max: 66) at visit 1, 60 (SD: 6, min: 49/max: 73) at visit 3, and 80 (SD: 7, min: 51/max: 97) at the end of follow-up. Mean age at diagnosis of dementia was 81 (SD: 6, min: 53/max: 96). At visit 1, individuals with high CVH had lower dementia risk compared to individuals with low CVH (HR: 0.60 [95% CI, 0.52–0.69]). In addition, there was a significant decrease in dementia risk per 1-point higher CVH score (HR: 0.93 [0.91–0.94]; Table 3). Similarly, at visit 3, individuals with high CVH had lower dementia risk compared to individuals with low CVH (HR: 0.63 [0.54–0.73]), and there was a decrease in dementia risk per 1-point higher CVH score (HR: 0.92 [0.90–0.93]; Table 3).

In AGES-Reykjavik, over a median follow-up of 10.5 years (interquartile range 8.3–11.6) starting from late-life, 972 (24.8%) participants were diagnosed with dementia. Participants had a mean age of 51 (SD: 6, min: 33/max: 83) at midlife and 85 (SD: 5, min: 71/max: 101) at the end of follow-up. Mean age at diagnosis of dementia was 86 (SD: 5, min: 71/max: 102). At the midlife visit, individuals with high CVH had lower dementia risk compared to individuals with low CVH (HR: 0.83 [0.66–0.99]). In addition, there was a significant decrease in dementia risk per 1-point higher CVH score (HR: 0.96 [0.92–0.99]; Table 3).

3.2 | Change in CVH within midlife

Kaplan–Meier curves for incident dementia by patterns of change in CVH are given in Figure S1 in supporting information. There was a decrease in dementia risk per 1-point increase in change in 14-point CVH score from visit 1 to visit 3 (HR: 0.94 [0.92–0.96]; Table 3). In addition, individuals who improved from moderate to high CVH and individuals with consistently high CVH at both visit 1 and 3 compared to individuals who had low CVH at both visits (consistently low; reference category) had the lowest risks (HRs: 0.51 [0.41–0.63] and 0.48 [0.39–0.58], respectively; Table 3 and Figure 3).

3.3 | Secondary analysis: CVH at late-life and change of CVH from midlife to late-life

Characteristics of participants included in the analysis on late-life CVH and details on follow-up in both cohorts are given in Table S3 in

TABLE 1 Definition of cardiovascular health metrics according to the American Heart Association in ARIC and AGES-Reykjavik

Metric	Recommended ideal level	Intermediate level	Poor level
Smoking[a]	ARIC: never or quit ≥12 months AGES-Reykjavik: never	ARIC: quit < 12 months AGES-Reykjavik: former	ARIC: current smokers AGES-Reykjavik: none
Body mass index[b]	Both studies: < 25 kg/m^2	Both studies: 25 to < 30 kg/m^2	Both studies: ≥30 kg/m^2
Physical activity[c]	ARIC: ≥75 min/week of vigorous activity, ≥150 min/week of moderate activity, or both AGES-Reykjavik: moderate or vigorous physical activities for > 180 min/week	ARIC: 1 to 74 min/week vigorous activity, 1 to 149 min/week moderate activity, or both AGES-Reykjavik: weekly moderate or vigorous physical activities, but ≤180 min/week	ARIC: None AGES-Reykjavik: rarely or never participated in physical activity
Healthy diet[d]	ARIC: ≥1 portion/day of each of fresh fruit, raw or cooked vegetables, and ≥2 portions/week of fish AGES-Reykjavik: not available	ARIC: ≥1 portion/day of each of fresh fruit, raw or cooked vegetables, or ≥2 portions/week of fish AGES-Reykjavik: not available	ARIC: < 1 portion/day of each of fresh fruit, raw or cooked vegetables, and < 2 portions/week of fish AGES-Reykjavik: not available
Blood pressure[e]	Both studies: < 120/80 mmHg, untreated	Both studies: < 120/80 mmHg on medications or 120-139/80-89 mmHg	Both studies: ≥140/90 mmHg
Fasting plasma glucose[f]	Both studies: < 100 mg/dL, untreated	Both studies:100 to < 126 mg/dL or < 100 mg/dL treated	Both studies: ≥126 mg/dL
Total cholesterol[f]	Both studies: < 200 mg/dL, untreated	Both studies: 200 to < 240 mg/dL or < 200 mg/dL treated	Both studies: ≥240 mg/dL

[a]In ARIC no information was available on months from quitting at visit 5, therefore defined as never, former, and current at late-life visit. In AGES-Reykjavik no information was available on months from quitting at both the midlife and late-life visit.
[b]Body mass index was calculated as weight in kilograms divided by height in meters squared.
[c]In ARIC determined by questionnaire at the midlife and late-life visits. In AGES-Reykjavik physical activity information for midlife and late-life was obtained at the AGES-Reykjavik study late-life visit by questionnaire. Subjects were questioned how often they participated in moderate or vigorous physical activities in the past 12 months and at midlife (age 50), as described previously.[36]
[d]In ARIC, diet was assessed with the 66-item Harvard food frequency questionnaire. Persons with extreme energy intake of < 600 or > 4200 kcal/day for men or < 500 or > 3600 kcal/day for women (approximate lower and upper 1 percentiles) were excluded. The following five items were used to designate an ideal diet: fruits and vegetables: ≥4.5 cups/day; fish: ≥two 3.5-oz servings/week; fiber-rich whole grains: ≥three 1-oz-equivalent servings/day; sodium: < 1500 per day; sugar sweetened beverages: ≤450 kcal (36 oz) per week. No diet data available at ARIC midlife visit 3.
[e]Blood pressure was measured three times (ARIC) or twice (AGES-Reykjavik) in a supine position after a 5-minute rest, with the average of the (last) two measurements used.
[f]Plasma glucose and total cholesterol were measured with standardized measures after an overnight fast. In AGES-Reykjavik no information available on lipid-modifying medications in midlife.
Abbreviations: AGES, Age, Gene/Environment Susceptibility; ARIC, Atherosclerosis Risk in Communities; min, minutes.

supporting information. In ARIC, over a median follow-up of 7.2 years (interquartile range 5.8–7.9) starting from visit 5 (late-life), 722 (14.4%) participants were diagnosed with dementia. Participants had a mean age of 52 (SD: 5, min: 51/max: 97) at visit 1, 75 (SD: 5, min: 69/max: 97) at visit 5, and 82 (SD: 5, min: 69/max: 97 at the end of follow-up. Mean age at diagnosis of dementia was 83 (SD: 5, min: 69/max: 97). In AGES-Reykjavik, over a median follow-up of 10.5 years (interquartile range 8.3–11.6) starting from late-life, 972 (24.8%) participants were diagnosed with dementia. Participants had mean age of 51 (SD: 7, min: 33/max: 83) in midlife and 76 (SD: 5, min: 66/max: 96) in late-life and 85 (SD: 5, min: 71/max: 101) at the end of follow-up. Mean age at diagnosis of dementia was 86 (SD: 5, min: 71/max: 102). At ARIC visit 5 (late-life), but not at AGES-Reykjavik late-life visit, there was a significant decrease in dementia risk per 1-point higher CVH score (ARIC HR: 0.93 [0.89–0.96]; AGES-Reykjavik HR: 0.96 [0.93–1.00]; Table S4 in supporting information). We did not find an association between per-point increase in CVH score over time and incident dementia in both studies (ARIC: HR: 0.95 [0.91–1.00]; AGES-Reykjavik: HR: 0.98[0.97–1.06]; Table S4).

3.4 | Sensitivity analyses

Table S5 in supporting information shows the association of each CVH metric at midlife with incidence of dementia. Excluding participants with history of cardiovascular disease did not change the findings (Table S6 in supporting information). The association between change in CVH within midlife and incidence of dementia was stronger in individuals who carry one or two *APOE* ε4 variants compared to those without (HR *APOE* ε4 carrier: 0.92 [0.90–0.95] vs. HR *APOE* other variants include (*APOE* ε3/ε3, *APOE* ε2/ε2, *APOE* ε2/ε3): 0.97 [0.95–0.99], *P* for interaction < 0.001; data not shown). Removing CVH metrics one by one from the CVH score did not show that a single component is driving the association (Table S7 in supporting information). Using

TABLE 2 Participant characteristics

	ARIC(n = 11,460)		AGES-Reykjavik (n = 3907)
General characteristics	**Midlife (visit 1)**	**Midlife (visit 3)**	**Midlife**
Age, mean (standard deviation), years	54.1 (5.7)	60.0 (5.7)	50.8 (6.5)
Men	5059 (44.1)	5059 (44.1)	1620 (41.5)
Education level[a]			
Basic	2202 (19.2)	2202 (19.2)	770 (19.7)
Intermediate	4835 (42.2)	4835 (42.2)	1885 (48.2)
Advanced	4412 (38.5)	4412 (38.5)	1252 (32.0)
Race			
Black	2293 (20.0)	2293 (20.0)	0 (0)
White	9167 (80.0)	9167 (80.0)	3907 (100)
Apolipoprotein E ε4 carrier status	3293 (28.7)	3293 (28.7)	1087 (28.0)
Diabetes	1034 (9.0)	1631 (14.3)	32 (0.8)
Cardiovascular disease[b]	612 (5.3)	914 (8.0)	71 (1.8)
Stroke	173 (1.5)	180 (1.6)	NA
Cardiovascular health status[c]			
Cardiovascular health score, median (range)	8 [7–10]	8 [6–10]	7 [5–8]
Cardiovascular health score categories			
Low (score ≤5, or ≤4)	1559 (13.6)	1516 (13.2)	491 (12.6)
Moderate (score 6 to 9, or 5 to 7)	6396 (55.8)	6905 (60.3)	2219 (56.8)
High (score 10 to 14, or 8 to 12)	3505 (30.6)	3039 (26.5)	1197 (30.6)
Ideal smoking score (%)	8574 (74.8)	9303 (81.2)	1594 (40.8)
Ideal BMI score (%)	3913 (34.1)	3186 (27.8)	2081 (53.3)
Ideal physical activity score (%)	4613 (40.3)	4791 (41.8)	776 (19.9)
Ideal diet score (%)	640 (5.6)	252 (2.2)	NA
Ideal total cholesterol score (%)	4209 (37.4)	4543 (39.6)	495 (12.7)
Ideal blood pressure score (%)	5034 (43.9)	3999 (34.9)	799 (20.4)
Ideal glucose score (%)	6133 (53.5)	5161 (45.0)	384 (98.3)

Note: Numbers indicate *n* (%) unless otherwise indicated.

Abbreviations: AGES, Age, Gene/Environment Susceptibility; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; NA, not available.

[a]In ARIC, education was self-reported at visit 1 as the highest grade completed in school and was categorized as basic education (less than high school completion), intermediate education (high school degree or vocational school), and advanced education (attending or completed college or professional school). In AGES-Reykjavik, education was categorized into three levels basic (elementary school), intermediate (high school degree), and advanced education (undergraduate and more than undergraduate education).

[b]In ARIC, cardiovascular events were ascertained via active surveillance of all participants in the study. Hospitalizations were identified through surveillance of hospitals within the study communities and reported by participants or their proxies during annual telephone calls. Study personnel abstracted potential cardiovascular events from hospital records. In AGES-Reykjavik, in midlife, participants were asked about history of cardiac disorders by a self-reported questionnaire. In late-life, history of cardiovascular disease was defined as coronary heart disease or stroke according to adjudicated Icelandic Heart Association registry or hospital records.

[c]The cardiovascular health metrics included non-smoking, and ideal levels of body mass index, physical activity, dietary habits, untreated blood pressure, fasting blood glucose, and total cholesterol. The continuous 12- or 14-point cardiovascular health score (higher score indicates better cardiovascular health) was calculated by assigning 0 points for poor metrics, 1 point for intermediate metrics, and 2 points for ideal metrics. Cardiovascular health score is calculated using seven items (14 point) at ARIC study visits 1 and 3 and using six items (not including dietary habits) at AGES-Reykjavik midlife visit. For more detailed definition of the cardiovascular health score, please see Table 1.

mortality as the outcome, we observed that a higher CVH score in midlife and improvement in CVH score within midlife is associated with lower mortality (Table S8 in supporting information). This suggests that the observed association with dementia is not due to higher mortality rates.

4 | DISCUSSION

In this analysis using data from two population-based studies, a higher CVH score in midlife and an increase in a CVH score over a median of 6 years within midlife were associated with a lower risk of

TABLE 3 Associations of cardiovascular health score at midlife and change of cardiovascular health score within midlife with incident dementia

Cardiovascular health score[a]	Number of events/total *N*	Hazard ratio[b] (95% CI)	Incidence rate, per 1000 person years(95% CI)
Midlife (ARIC visit 1)			
Low (score 0 to 5)	355/1559	1 [Reference]	14.3 (12.8, 15.8)
Moderate (score 6 to 9)	1328/6396	0.72 (0.64, 0.81)	11.1 (10.5, 11.7)
High (score 10 to 14)	581/3505	0.60 (0.52, 0.69)	7.9 (7.3, 8.6)
Per 1-point higher in the cardiovascular health score	2264/11,460	0.93 (0.91, 0.94)	10.4 (10.0, 10.8)
Midlife (ARIC visit 3)			
Low (score 0 to 5)	302/1516	1 [Reference]	12.0 (10.7, 13.4)
Moderate (score 6 to 9)	1430/6905	0.78 (0.69, 0.89)	11.0 (10.4, 11.6)
High (score 10 to 14)	532/3039	0.63 (0.54, 0.73)	8.6 (7.8, 9.3)
Per 1-point higher in the cardiovascular health score	2264/11,460	0.92 (0.90, 0.93)	10.4 (10.0, 10.8)
Midlife (AGES-Reykjavik midlife visit)			
Low (score 0 to 4)	131/491	1 [Reference]	29.4 (24.6, 34.9)
Moderate (score 5 to 7)	594/2219	0.94 (0.77, 1.14)	27.9 (25.6, 30.2)
High (score 8 to 12)	247/1197	0.83 (0.66, 0.99)	20.3 (17.8, 23.0)
Per 1-point higher in the cardiovascular health score	972/3907	0.96 (0.92, 0.99)	24.0 (25.6, 27.3)
Change within midlife (from ARIC visit 1 to visit 3)			
Constantly low	160/711	1 [Reference]	14.7 (12.4, 16.9)
Low to moderate/high	195/848	0.76 (0.61, 0.93)	14.0 (12.0, 16.0)
Moderate to low	136/768	0.66 (0.52, 0.83)	10.1 (8.4, 11.8)
Constantly moderate	993/4662	0.62 (0.53, 0.74)	11.4 (10.7, 12.1)
Moderate to high	199/966	0.51 (0.41, 0.63)	10.7 (9.2, 12.1)
High to low/moderate	254/1465	0.54 (0.44, 0.66)	8.4 (7.4, 9.4)
Constantly high	327/2034	0.48 (0.39, 0.58)	7.6 (6.8, 8.4)
Per 1-point increase in change in cardiovascular health score[c]	2264/11,460	0.94 (0.92, 0.96)	10.4 (10.0, 10.8)

Abbreviations: AGES, Age, Gene/Environment Susceptibility; ARIC, Atherosclerosis Risk in Communities; CI, confidence interval.
[a]For definition of the cardiovascular health score (six and seven items), please see Table 1.
[b]Hazard ratios and 95% confidence intervals were estimated by Cox proportional hazard models using age as the time scale. Models are adjusted for education level, sex, and race plus center (in ARIC).
[c]Further adjusted for baseline (visit 1) cardiovascular health scores. There was on average 6 years between visit 1 and visit 3 in the ARIC study.

dementia in late-life. Our secondary analysis on CVH at late-life and change in CVH between midlife and late-life, however, showed less consistent associations with risk of dementia. Our findings suggest that midlife primordial prevention of cardiovascular risk factors is a protective factor for incident dementia.

The current findings are in line with previous population-based studies that demonstrated an association between higher CVH at midlife and incident dementia.[5,6,8,10,30] However, it remained unclear whether change in CVH is associated with risk of dementia. Randomized trials investigating the effect of multi-faceted cardiovascular risk factor intervention on cognitive decline are scarce, only included relatively older individuals, and had inconsistent findings. The Finnish Geriatric Intervention to Prevent Cognitive Impairment and Disability (FINGER) trial showed that, among individuals with a mean age of 69, a multidomain lifestyle intervention can have a small beneficial effect on cognitive function.[31] The Prevention of Dementia by Intensive Vascular Care (preDIVA) trial including individuals with a mean age of 75 did not find a beneficial effect of a multidomain vascular intervention on dementia risk.[32] Only one previous observational study, the Finnish Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study,[8] evaluated change in CVH over time with risk of dementia. This study did not find an association between change in CVH between midlife (age 50) and late-life (age 70) and risk of dementia. This study had a relatively small sample (n = 744; only 47 dementia cases) and short follow-up (mean 8 years).

Our results suggest that greater adherence to CVH recommendations over time within midlife might be beneficial for the prevention of dementia at older age. Individuals who improved their CVH within midlife had lower dementia risk with reductions in the risk of dementia across the continuum of the 14-point CVH score. This highlights

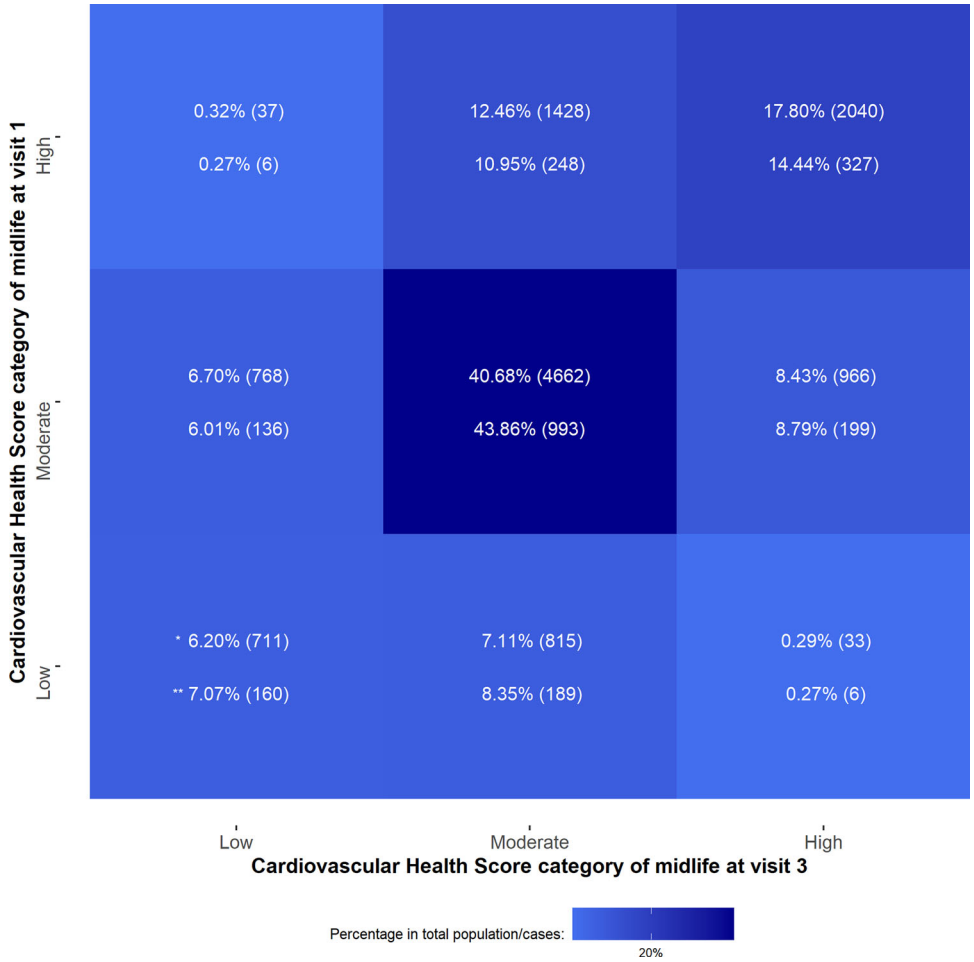

FIGURE 3 Heatmap of number and percentage of participants and dementia cases in cardiovascular health status category within midlife in Atherosclerosis Risk in Communities ($n = 11{,}460$). *Percentage (number) of participants in total population. **Percentage (number) of dementia cases among all dementia cases. Darker color indicates higher percentage.

the importance of primordial prevention of a set of cardiovascular risk factors in midlife for risk of dementia at older ages. This study thereby supports public health policies to improve CVH within midlife to promote prevention of dementia.

There was no consistent relationship between CVH at late-life and change in CVH between midlife and late-life and risk of dementia. For instance, individuals who changed from low CVH at midlife to moderate or high CVH at late-life did not have a lower risk of dementia compared to individuals who had consistently low CVH over time in either ARIC or AGES-Reykjavik. These observations are across different cohorts and geographic locations and participants aged during different periods. Similar observations in both studies suggest that these negative associations are less likely explained by any period or cohort effect. Given the long preclinical phase of dementia, prognosis may be determined primarily by CVH early in life. This would suggest that promotion of CVH at late-life is less beneficial to prevent the risk of dementia. However, other reasons may explain this finding. First, results on late-life CVH may have been affected by reverse causality, that is, dementia has a long preclinical phase[33] that may be present at the late-life visits of both studies and may affect risk factors. Second, the relatively long interval between the examinations at midlife and at late-life in both studies may have led to attrition bias with a disproportional loss of people during follow-up who were in worse health and at higher risk for dementia. This may have led to inclusion of more healthy participants in the analyses on late-life CVH compared to participants who were included only in the analyses on midlife CVH. These biases may have led to an underestimation of the reported associations. Third, given that the causal network for dementia is complex, there may be many unmeasured confounding and mediating variables embedded within the data in this study. The analysis on change between midlife and late-life may be particularly vulnerable for this bias. For example, it is likely that some individuals received treatment of cardiovascular risk factors between the long time interval between midlife and late-life. Fourth, some categories of CVH were small in size, potentially explaining why some associations did not reach statistical significance (e.g., only 159 participants in ARIC improved from low CVH in midlife to moderate or high CVH in late-life).

The AHA approach was developed for primordial prevention of cardiovascular risk factors and thus should not be interpreted as the best summary of existing epidemiologic knowledge for preventing

dementia. Future studies are needed to evaluate differential weighting of metrics and of potential interaction between metrics and dementia risk. Nevertheless, our additional analysis did not show that an individual metric of the CVH score drives the association between CVH and incident dementia, and suggests that it is rather the combination of the items that is important. Of the individual CVH metrics at midlife, physical activity was associated with incident dementia in ARIC, but not in AGES-Reykjavik. Physical activity at midlife in AGES-Reykjavik was based on recalled data at the late-life visit, which may have led to measurement error bias. Dietary habits and total cholesterol were also not associated with incident dementia. Previous studies on dietary habits and total cholesterol and risk of dementia also report inconsistent results,[34,35] and this requires further study.

The present study has limitations. First, the observational design precludes reaching causal conclusions. As with any observation study, our results might be susceptible to residual confounding. For example, some risk factors are more prevalent among persons of lower socioeconomic status, and adjustment for education may not capture that potential confounding completely. Second, individuals excluded from the analysis of change in CVH were older and had a less favorable cardiovascular risk profile (Table S2), which may have led to an underestimation of the reported associations. Third, attempts were made to minimize missed cases of dementia, but the accuracy of dementia cases detected by vital statistics or hospital records may be less good than the cases detected by in-person neuropsychological assessment. It is possible that dementia cases identified through death certificates or hospitalization codes may be incorrect or may be more frequent in individuals with a higher cardiovascular risk. This may have led to an overestimation of the association between CVH and incident dementia. Also, misclassified cases might lead to an underestimation of associations between CVH and dementia. Fourth, data on dietary habits were not available at the ARIC late-life visit and the AGES-Reykjavik midlife and late-life visits. Fifth, the generalizability of this study may be limited given that the study sample consisted of Black and White individuals from four selected US communities and White individuals from Iceland.

In conclusion, higher CVH and improvement in CVH within midlife were associated with a lower risk of dementia. These findings may have important public health implications highlighting the need for promotion and maintaining ideal CVH at midlife to reduce risk of dementia.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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