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RESEARCH NOTES

Comparing the educational gradients in three cardiovascular disease-specific health measures

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Less-educated persons have worse cardiovascular health. We compare the educational gradients in three disease-specific health measures (biomarkers, self-reported doctors' diagnoses and cause-specific mortality) in order to compare their relevance in different stages of the disease process. We study 14,102 people aged 50–89 from the US Health Retirement Study (HRS) in the period 2006–17. We use six CVD biomarkers (systolic/diastolic blood pressure, ratio total/HDL cholesterol, C-reactive protein, body mass index, HbA1c) and two self-reported doctors' diagnoses (stroke, heart attack). We estimate the gradient in biomarkers using log-binomial regression and the hazard of diagnoses and CVD mortality with Cox survival models.

Among those without pre-diagnosed CVD conditions, the educational gradient in mortality is highest (RR 1.97), the gradient for those who receive a CVD diagnosis is in the middle (RR 1.46), and the gradient in biomarkers is lowest (RR 1.32). Among those with recent/older diagnoses, the biomarker gradient is comparable to levels among the non-diagnosed, while the mortality gradient is much lower (RR 1.35). The gradients in diagnoses and mortality are only slightly explained by differences in biomarkers.

The comparison of the three gradients and the mediation analysis suggest that in each of the steps to diagnosis and death there are social factors involved that increase the gradient and go beyond what biomarkers can predict. Having a CVD diagnosis leads to smaller mortality gradients, presumably because of the convergence of educational differences in behaviour and during treatment and monitoring. Our findings support prevention as a strategy against social inequalities in CVD.

Key words health inequality • cardiovascular diseases • biomarker • mortality • Health and Retirement Study (HRS)

Key messages

- The educational gradient is highest for mortality; next highest is diagnoses; lowest is biomarkers.

- The gradients in diagnoses and mortality are only slightly explained by differences in biomarkers.
- CVD progression is subject to social factors that widen the gradient beyond biomarkers' predictivity.
- Among diagnosed people, changes in behaviour and treatment seem to lower the mortality gradient.

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Introduction

The social gradient in cardiovascular disease (CVD) is well established. We compare three educational CVD gradients in relative risk, based on three different measures of CVD, namely biomarkers, doctors' diagnoses and mortality. These health measures can be considered to represent different stages of the disease process: first, biomarkers can reveal subclinical risks in patients without a CVD diagnosis. Educational differences in biomarkers can be due to, for example, health-related behaviours and differential (cumulative) exposures to risk factors. Second, diagnoses are the next step to a recognisable problem, awareness, communication and potential treatment. Diagnoses are influenced by health literacy, seeking care and clear communication with the doctor. Third, mortality (with or without prior diagnosis) is the final stage of the deterioration of the condition. Once again, education can make a difference by increasing health literacy so that treatment is better adhered to. We aim to find out when in the disease process the social gradient arises and what the use of biomarkers in social surveys can add to our understanding of health inequalities. The general hypothesis for our study posits that the educational gradient increases over the course of the disease process, because education influences it at each step. This would imply that the educational gradient is smallest for biomarkers (especially in the pre-diagnosis phase), larger for doctors' diagnoses and larger again for CVD mortality.

Many large-scale population surveys have included biomarkers that have been shown in prior (clinical) research to predict cardiovascular disease, as this constitutes the major cause of death in midlife and old age in most developed countries and also in the US (Murray and Lopez, 1997; Lozano et al, 2012; Heron, 2013). The study of biomarkers offers two important advantages over the reliance on traditional measures of health: first, biomarkers can be used as indicators of preclinical risks at an early stage; second, they are (just like mortality) objective indicators that are not biased by access to medical services, perceptions, reporting and health literacy (Lindau and McDade, 2008; Aiello and Kaplan, 2009; Layard, 2010). Beyond the use of biomarkers, it is still important to take the potential treatments and behavioural changes into account that a diagnosis of a stroke or heart attack (if survived) can induce. If they occur differently in different educational groups, they can influence the social gradient in subsequent levels of biomarkers and in mortality.

Taking advantage of the complementary nature of biomarkers and doctors' diagnoses, we compare educational differences in biomarkers to educational

differences in diagnoses and mortality to estimate the relevance of education at different stages of the disease process. This enables an exploration of how social gradients in CVD develop over time and whether social differences play a significant role in the reaction to a diagnosis. We also estimate whether a relevant part of the educational gradient in CVD diagnoses and mortality can be explained by the differences in biomarkers. Education can affect CVD biomarkers by health behaviour and the level of psychosocial stress (Dinwiddie et al, 2016), among other mechanisms (de Mestral and Stringhini, 2017). The biological effects of psychosocial stress that may contribute to social differences in CVD have been described with the concept of allostatic load, which means the physiological ‘wear and tear’ during the life course (Delpierre et al, 2016, Johnson et al, 2017).

Our study contributes to a better understanding of when the social gradient in CVD arises and how newly available data on biomarkers can be used to shed light on unknown early stages in the disease process. This is important for developing possible intervention strategies to improve cardiovascular health and decrease the social gradient in CVD.

As a general framework of the interdependencies between education, CVD biomarkers and cardiovascular health, we refer to the following general model, which we adopted from Aiello and Kaplan (2009) and slightly modified (Figure 1). It shows, first, the position of our variables in the pathway from education via biomarkers (measuring the dysregulation in the centre of the model) to health and mortality and, second, the steps between these variables that we cannot investigate in this study. As already mentioned, education has a substantial effect on health via lifestyle behaviours, problem-solving abilities, and values. It facilitates the acquisition of economic skills and assets, and may increase resilience, self-esteem and self-efficacy. Our choice of biomarkers will be explained in detail in this paper, as well as our two measures of cardiovascular health: doctors’ diagnosis and mortality.

Data and methods

We use data from the HRS, a survey of the general household population aged 50+ in the US (Sonnega et al, 2014). In our analyses we use both the harmonised HRS data set from RAND (RAND, 2019) and sensitive health data on biomarkers (Health and Retirement Study, 2013). The HRS is sponsored by the National Institute on Aging (grant number NIA U01AG009740). In the HRS, blood-based, CVD-related biomarkers were collected using the dried blood spot method (Crimmins et al, 2014). We use the first available measurement of blood spots for each person (one of 2006, 2008 or 2010) using an adjustment for dried blood spots to be comparable to measures taken from venous blood (Crimmins et al, 2013). The year of the first available blood spot measure is the baseline for our analysis, which results in a maximum of 11 years follow-up (2006–17) to assess CVD-specific diagnoses and mortality. We restrict our sample to those in the age range of 50–89 at the time of biomarker measurement. After excluding 593 respondents who did not take part in the biomarker measurements and 628 respondents without valid vitality status, the sample size is 14,102. In all analyses we use weights provided by HRS to account for differential participation in the blood-based biomarker measurements.

We found a substantial number of missing values on at least one of our six biomarkers (3,422; 19%). To address this problem, we conducted multiple imputation, using

chained equations including all other variables. We use 50 imputed data sets for all of our estimates.

Education was measured in three categories: some college or higher (reference category), high school and no high school degree. From all available biomarkers in HRS we selected those that are established biomarkers for CVD. For documentation, see [Crimmins et al \(2013\)](#), and [Benzeval et al \(2014\)](#) for further explanations of biomarkers. We used the following biomarkers and cut-off points (in brackets):

- 1 Ratio of total to high-density-lipoprotein cholesterol (HDL, >5)
- 2 Glycated haemoglobin (hbA1c, $\geq 6.4\%$)
- 3 C-reactive protein (CRP, $\geq 3 \mu\text{g/ml}$)
- 4 Systolic blood pressure (SBP, $>139 \text{ mmHg}$)
- 5 Diastolic blood pressure (DBP, $>89 \text{ mmHg}$)
- 6 Body mass index (BMI, $\geq 35 \text{ kg/m}^2$)

From the six biomarkers, we calculate an index ranging from 0 to 6. Because the number of people with six biomarkers is very small (21), and because we use the biomarker index as a categorical predictor in the mediation analysis, we collapsed those with five and six biomarkers, resulting in an index ranging from 0 to 5. In principle, information is lost when combining biomarker items into an index; for example, not all biomarkers take part in the same aetiological pathway. However, a simple risk index has been shown to be a good compromise between complexity and predictive power with respect to CVD mortality ([Kröger and Hoffmann, 2018](#)). For doctors' diagnoses, we use two binary variables containing the earliest self-reported doctors' diagnosis of stroke and heart attack. The mortality analysis takes into account all deaths due to CVD. Information about the vitality status of an individual is collected with exit interviews, typically with a surviving spouse or child ([Weir, 2016](#); [Fisher and Ryan, 2018](#)). We estimate the gradient in biomarkers using log-binomial regression, and Cox survival models for the gradient in the hazard of diagnoses and CVD mortality (for more details, see Appendix). Both model types yield relative rates as the scale for the coefficients. The coefficients of the log-binomial model can be interpreted as the relative rate of prevalence of biomarker risk factors at baseline time, and the coefficients of the survival models as relative hazard rates of the incidence of a doctors' diagnosis, or CVD mortality, respectively. We use the term rate ratio (RR) to abbreviate both throughout the manuscript. The models control for gender, age at baseline, and ethnicity (White vs non-White).

We model the diagnoses of stroke and heart attack as an incidence rather than a prevalence, similar to the event of death. This means we measure when people receive a new diagnosis, which entails that we can only compare the three educational gradients in biomarkers, diagnoses and mortality among healthy people, that is, currently without any CVD-related diagnosis. We split our sample and our analysis into the resulting three diagnosis groups at baseline: (1) 'healthy' people (without any CVD-related diagnosis), (2) those with a recent diagnosis (in the last two years) and (3) those with an older diagnosis. This allows us to stratify the analysis along a time dimension that reflects important steps in the disease process and reveals (1) differences in the educational gradients in three health measures and (2) differences in these gradients between stages of the disease process.

Results

Table 1 shows that all six biomarkers have a significant prevalence, between 16% and 38%. On average, respondents have 1.42 biomarker risk factors. The incidence rate of having a doctors' diagnosis in the follow-up period is 13% and the risk of dying of CVD is 8%. All health indicators show the expected educational gradient, with higher risks among the less educated. The overall educational distribution shows a highly educated population. The more detailed Appendix Table A1 shows that older cohorts and the non-White population are less educated and, at least concerning the share of people with a college degree, women are also less educated than men.

As explained earlier, we separate the analysis into the healthy, the recently diagnosed and those with older diagnoses, referring to t_0 as the time of first biomarker measurement. Figure 2 shows standardised (for age and gender) mortality rates per year (SMR) for all combinations of diagnosis status (healthy, recent, older) and biomarkers (0, 1, 2 and 3+ BM). Having a recent diagnosis, that is, having (survived) a heart attack or a stroke, statistically significantly increases the risk of dying of CVD. An older diagnosis implies a lower mortality risk than a recent diagnosis, but higher than for healthy people. Within each of these three groups, having more biomarkers is associated with higher mortality. This results in a maximum difference in mortality risk per year between healthy people without biomarkers (SMR: 0.004) and those with a recent diagnosis and two or more biomarkers (SMR: 0.032).

Figure 3 shows the main results in graphical form. The educational gradient in biomarkers is roughly the same in all three groups of the sample, that is, it does not change when people get a diagnosis or when this diagnosis gets older. This is different from the educational gradient in mortality, which is substantially higher among the healthy (RR: 1.97) than among those with a recent diagnosis (RR: 1.36) or an old diagnosis (RR: 1.34). In other words, reporting a diagnosis (which implies survival) ameliorates social differences in mortality, but the educational gradient in the biomarkers remains almost constant. Among healthy people, we see a clear difference between a relatively low educational gradient in biomarkers (RR: 1.32), a somewhat higher gradient in diagnoses (RR: 1.46), and a high gradient in mortality (RR: 1.97).

Table 2 adds a mediation analysis to the results in Figure 2 that reveals how much of the educational gradients in the diagnoses and mortality can be explained by biomarkers. In the four models (four columns) that control for biomarkers, the control reduces the uncontrolled educational gradient by 15% to 35%. Thus, the gradients in diagnoses and mortality can only be partly explained by initial differences in biomarkers, and the mediation of the effect of education on diagnoses or mortality via biomarkers is modest. Another potential mediator between education and CVD outcomes is use of medication. This variable is more complex, since it can be both a mediator and a confounder at the same time. When included into the model, the results are almost identical. The results and explanations of this variable are in Appendix Figure A1.

Discussion

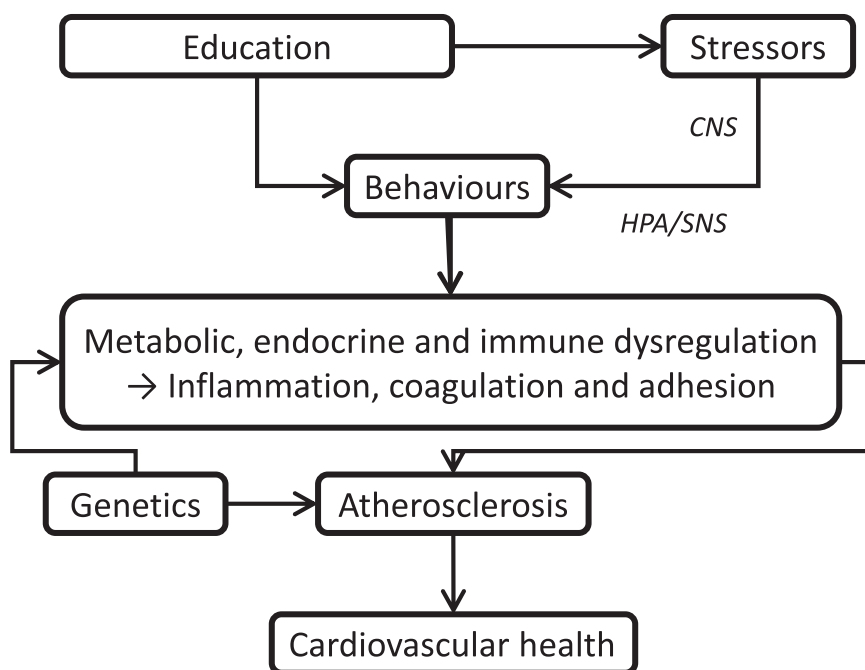
This study compares the educational gradient in three CVD-specific health measures. We found, *first*, that all health measures exhibit a clear educational gradient: the biomarker index, diagnoses of stroke and heart attack, and CVD mortality. *Second*,

Table 1: Summary statistics with prevalences of biomarkers, doctors' diagnoses and mortality (by education)

	All			No High School			High School			Some College		
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Age at baseline	66.9	9.64	51.0	89.0	69.0	9.62	51.0	89.0	67.6	9.45	51.0	89.0
Non-White	0.22	0.42	0.00	1.00	0.36	0.48	0.00	1.00	0.19	0.39	0.00	1.00
Gender = male	0.42	0.49	0.00	1.00	0.41	0.49	0.00	1.00	0.39	0.49	0.00	1.00
High ratio of TC to HDL (>5)	0.22	0.42	0.00	1.00	0.25	0.43	0.00	1.00	0.24	0.42	0.00	1.00
High hbA1c (>=6.4%)	0.16	0.37	0.00	1.00	0.23	0.42	0.00	1.00	0.16	0.37	0.00	1.00
High CRP (>=3.0 µg/mL)	0.38	0.49	0.00	1.00	0.45	0.50	0.00	1.00	0.40	0.49	0.00	1.00
High systolic BP (>139 mmHg)	0.32	0.47	0.00	1.00	0.39	0.49	0.00	1.00	0.32	0.47	0.00	1.00
High diastolic BP (>89 mmHg)	0.20	0.40	0.00	1.00	0.22	0.42	0.00	1.00	0.20	0.40	0.00	1.00
High BMI (>= 35 kg/m ²)	0.17	0.37	0.00	1.00	0.19	0.39	0.00	1.00	0.17	0.38	0.00	1.00
No biomarker	0.28	0.45	0.00	1.00	0.19	0.39	0.00	1.00	0.25	0.43	0.00	1.00
1 biomarker	0.30	0.46	0.00	1.00	0.30	0.46	0.00	1.00	0.31	0.46	0.00	1.00
2 biomarkers	0.23	0.42	0.00	1.00	0.25	0.43	0.00	1.00	0.24	0.43	0.00	1.00
3 biomarkers	0.13	0.33	0.00	1.00	0.17	0.37	0.00	1.00	0.13	0.33	0.00	1.00
4 biomarkers	0.05	0.22	0.00	1.00	0.07	0.26	0.00	1.00	0.05	0.22	0.00	1.00
5-6 biomarkers	0.02	0.13	0.00	1.00	0.03	0.16	0.00	1.00	0.02	0.13	0.00	1.00
Biomarker index	1.42	1.25	0.00	5.00	1.72	1.29	0.00	5.00	1.47	1.23	0.00	5.00
Diagnosed heart attack / stroke	0.13	0.34	0.00	1.00	0.17	0.37	0.00	1.00	0.15	0.35	0.00	1.00
Diagnosed heart attack	0.05	0.22	0.00	1.00	0.07	0.25	0.00	1.00	0.06	0.24	0.00	1.00
Diagnosed stroke	0.09	0.28	0.00	1.00	0.12	0.32	0.00	1.00	0.10	0.30	0.00	1.00
Medication against CVD	0.47	0.50	0.00	1.00	0.53	0.50	0.00	1.00	0.51	0.50	0.00	1.00
Death from CVD	0.08	0.27	0.00	1.00	0.11	0.32	0.00	1.00	0.08	0.28	0.00	1.00
Death from other causes	0.12	0.32	0.00	1.00	0.17	0.37	0.00	1.00	0.12	0.33	0.00	1.00
Observations	14,102				2,822 (20.0%)				4,965 (35.2%)			
										6,313 (44.8%)		

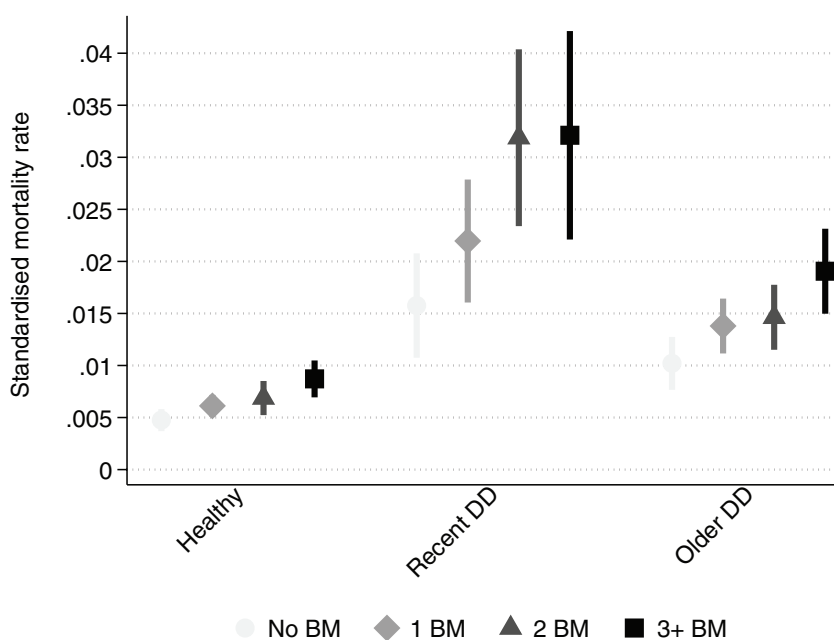
Note: SD = standard deviation.

Figure 1: Pathways between education, biomarkers and cardiovascular health.



Notes: CNS = central nervous system; HPA = hypothalamic–pituitary–adrenal axis; SNS = sympathetic nervous system.

Figure 2: Standardised mortality rates for healthy individuals, the recently diagnosed and those with older diagnoses.



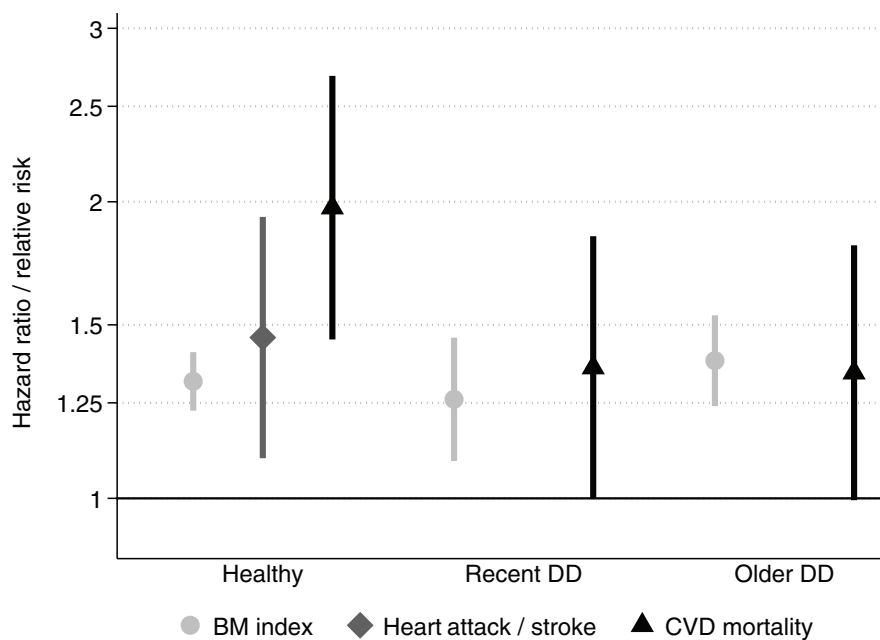
Notes: DD = diagnosis; BM = biomarker.

Table 2: Rate ratios for biomarkers (BM), doctors' diagnoses (DD) and mortality (with and without control for BM)

	Healthy (n = 9,385)						Recent DD (n = 1,563)						Old DD (n = 3,154)					
Education	BM	DD	DD+BM	Mort	Mort+BM	BM	Mort	Mort+BM	BM	Mort	Mort	BM	Mort	Mort+BM				
No high school	1.32 (1.24–1.41)	1.46 (1.10–1.93)	1.37 (1.03–1.82)	1.97 (1.45–2.68)	1.83 (1.34–2.50)	1.27 (1.11–1.47)	1.36 (1.00–1.85)	1.29 (0.94–1.77)	1.39 (1.25–1.54)	1.34 (1.00–1.81)	1.22 (0.90–1.66)	1.39 (1.25–1.54)	1.34 (1.00–1.81)	1.22 (0.90–1.66)				
High school	1.17 (1.11–1.24)	1.30 (1.04–1.63)	1.26 (1.00–1.58)	1.71 (1.31–2.24)	1.64 (1.25–2.15)	1.17 (1.02–1.33)	1.23 (0.91–1.66)	1.17 (0.86–1.59)	1.27 (1.15–1.40)	1.13 (0.85–1.50)	1.09 (0.82–1.45)	1.27 (1.15–1.40)	1.13 (0.85–1.50)	1.09 (0.82–1.45)				
Some college	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
5 Biomarkers			2.21 (1.14–4.32)		4.14 (1.98–8.67)			1.71 (0.52–5.65)						4.33 (1.88–9.98)				
4 Biomarkers			1.61 (0.94–2.77)		2.10 (1.14–3.85)			1.86 (0.95–3.65)						2.14 (1.18–3.87)				
3 Biomarkers			1.62 (1.12–2.34)		1.61 (1.04–2.48)			1.84 (1.11–3.07)						1.47 (0.92–2.34)				
2 Biomarkers			1.46 (1.03–2.07)		1.49 (1.00–2.20)			1.70 (1.09–2.67)						1.43 (0.95–2.17)				
1 Biomarker			1.29 (0.94–1.78)		1.32 (0.92–1.88)			1.44 (0.96–2.17)						1.30 (0.88–1.92)				
0 Biomarkers			1		1			1						1				

Note: Bold print = statistically significant ($p < .05$)

Figure 3: Rate ratios for educational groups (no high school vs some college) for biomarkers, doctors' diagnoses and mortality; among the healthy, recently diagnosed and older diagnoses.



Notes: DD = diagnosis; BM = biomarker.

comparing those without and those with a serious CVD diagnosis (be it recent or older), the educational gradient in biomarkers is on the same low level, while the mortality gradient is much higher among the healthy. *Third*, among the healthy, the educational gradient in mortality is higher than the gradient in diagnoses, which again is higher than the gradient in biomarkers. *Fourth*, the gradient in diagnoses and CVD mortality is only explained to a small degree by initial differences in biomarkers.

The *first finding* replicates a well-established finding from numerous studies in the past (for instance, [Kilander et al, 2001](#); [Aiello and Kaplan, 2009](#)). It serves as a precondition for our aim to compare educational gradients in different health measures and at different stages of the disease process. The *second finding* suggests that deaths from undiagnosed CVD conditions are very unequally distributed. By undiagnosed, we mean undiagnosed at the time of the interview preceding death. This finding includes differential survival rates of heart attacks and strokes, for example. However, once people are given a diagnosis of a serious CVD condition, the system and regime of intensive treatment in highly developed health systems have an equalising effect ([Hoffmann, 2011](#)), because their effects dominate the unequally distributed individual 'private' everyday behaviour. If this proposed mechanism is correct, it seems to reduce excess deaths among the less educated by preventing them, while it does not reduce the social gradient in biomarkers as a measure of the underlying physiological status.

The *third finding* warrants another differentiated view on the educational gradient in CVD, which generally can be measured in different indicators of CVD (for

example, in [Metcalf et al, 2008](#)): among the healthy, we see the lowest gradient in the biomarkers, which is supposed to measure the objective biological level of risk. Educational differences in actually experiencing a stroke or a heart attack and having it diagnosed are somewhat higher, albeit not statistically significantly. Finally, the mortality gradient is significantly higher. The increase of the gradient in these two steps suggests that, at each step, additional social factors play a role that disadvantage less-educated people. These factors may be structural or behavioural factors that create a higher risk of CVD conditions or mortality for less-educated people, on top of their elevated level of biomarkers.

This interpretation is confirmed by our *fourth finding* from the mediation analysis. The biomarkers included in our study do not explain a large fraction of educational differences in diagnoses and mortality. We assume that an ideal and very comprehensive set of biomarkers could explain more of the social gradient in CVD disease and mortality. But it is also likely that there would still remain a social difference which, on any given level of biomarker risk, could be due to differences in how people react to symptoms or diagnoses, or how they and their social environment react in acute situations.

This modest explanatory power of a few easy biomarkers, as used here, also implies that mass screening and the use of biomarkers in surveys for the purpose of explaining and preventing social inequalities in health is limited. Such an approach might be useful if combined with behavioural and contextual variables that shed light on additional factors and risk exposures.

Limitations

First, the comparison of gradients between groups with and without a diagnosis of a severe CVD condition is subject to mortality selection bias. The surviving population is more homogenous and might also have unobserved biological and behavioural factors of resilience. While some of the difference in the educational mortality gradient between these two groups might be explained by this bias, it is interesting that the gradient in biomarkers is stable across these groups, which suggests that the bias does not explain too much of the difference. Further, we cannot rule out that both educational level and CVD in old age are the joint result of third factors, possibly resulting from early childhood, including health-related selection ([Hoffmann et al, 2018](#)).

Second, since we only have data from interviews every other year, we have to categorise a death without prior diagnosis if no diagnosis was mentioned in the last interview before death. There might have been a diagnosis between this interview and the time of death. A different but related problem is that deaths in the ‘healthy’ group may include people who are not insured and could not pay for the doctor even if they had symptoms.

Third, CVD does not stand alone. Multimorbidity is common, especially in advanced age, and many respondents might be obese, have diabetes, COPD and so on. These conditions are not covered by our analysis, although they might influence biomarker levels and the incidence of CVD. They can also influence CVD mortality in complex ways, by increasing it, by functioning as competing risks that decrease CVD mortality, and by contributing to a certain fuzziness of death records, where,

especially in advanced age, CVD may be used a residual category for deaths with unclear or multiple causes.

Fourth, as mentioned earlier and shown in Appendix [Table A1](#), the educational distribution is different for different cohorts and the relative size of the educational groups in principle affects the rate ratios in our analysis. However, it is not our aim to compare rate ratios between age groups and we control for age.

Fifth, due to small sample sizes, we decided to focus on a joint analysis for men and women, but provide separate analyses in the Appendix [Figures A2a–A3b](#). They show that there are slight differences between men and women. For example, the educational gradient in diagnoses is not larger than the gradient in biomarkers for men. But these gender differences are subject to a high degree of uncertainty and cannot be sensibly interpreted on such a low level of statistical power. Gender differences, therefore, remain open for future investigation.

Conclusion

The comparison of the three gradients and the results of the mediation analysis suggest that in each step, from non-diagnosed to diagnosis and from diagnosis to death, there are social factors involved that increase the educational gradient. These factors go beyond what biomarkers can measure, so they should be used as an additional unique piece of early and objective information on the CVD process. They should, however, preferably be complemented by information on social factors that explain why people with the same level of biomarkers have different risks of CVD and death. Our finding that receiving a CVD diagnosis implies smaller mortality gradients suggests that intensive medical treatment may decrease the social gradient. However, social factors in everyday life – which create the unequal onset and development of CVD in the first place – should be the main target for improved prevention of social inequalities in CVD.

Note

The authors take responsibility for the integrity of the data and the accuracy of the analysis. The data is not publicly available.

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Conflict of interest

The authors declare that there is no conflict of interest

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Appendix

Calculation of the standardised mortality rates (SMR) in Figure 2

The adjustment follows the idea of presenting the mortality results of all categories (k , defined by education and the number of biomarkers in this study) relative to the expected incidences of mortality based on the person-time distribution within strata specific to gender and age groups (i). The standardised mortality rate ($R_{k,s}$) is then defined as (Rothman et al, 2008: 49):

$$R_{k,s} = \frac{\sum_{i=1}^j T_i R_{k,i}}{\sum_{i=1}^j T_i}$$

In this notation, i indexes the categories and $R_{k,i}$ is the group-specific rate, while T_i is the weight for each group derived from the so-called standard population. For the standard population, we use the person-time found in each stratum i across all categories k .

Calculation of the regression models

For the educational gradient in the biomarker index, we use log-binomial models, defined as:

$$\log(BM) = \alpha + \sum_{\substack{edu = \\ \{no\ HS, HS\}}} \beta_{edu,BM} D_{edu} + X\gamma_{BM}$$

Note that we report exponentiated coefficients ($\exp(\beta)$) throughout the paper and in the figures.

In this model X is the matrix of control variables, γ the corresponding coefficient vector. D_{edu} is a set of two dummy variables that have the value 1 if the individual has no high school (HS) or high school, respectively. The reference category which is omitted is ‘some college’. Using the same notation, the Cox models for the hazard of a doctors’ diagnosis and mortality are:

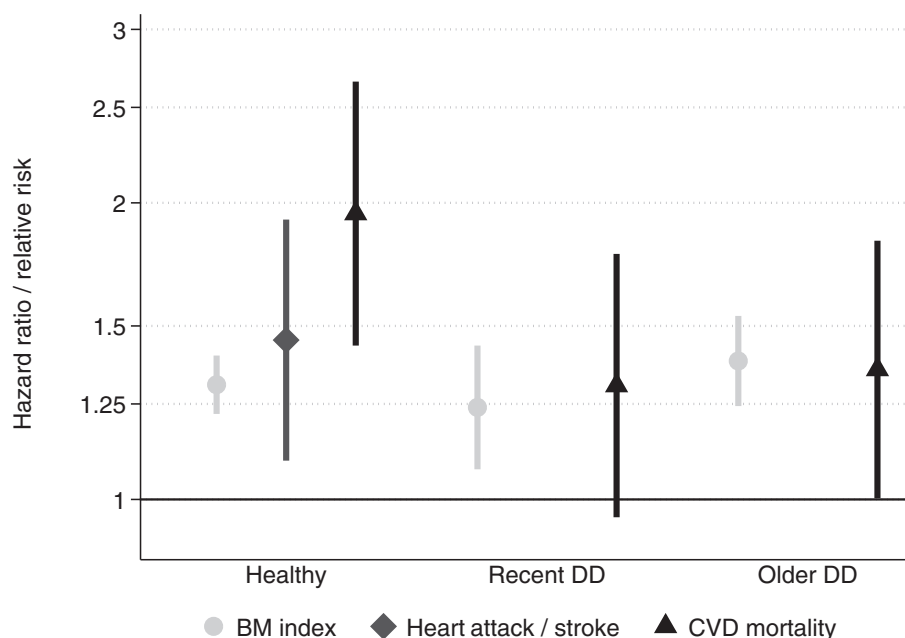
$$h_{DD}(t) = h_{0,DD}(t) \exp\left(\sum_{\substack{edu = \\ \{no\ HS, HS\}}} \beta_{edu,DD} D_{edu} + X\gamma_{DD}\right)$$

$$h_{mort}(t) = h_{0,mort}(t) \exp\left(\sum_{\substack{edu = \\ \{no\ HS, HS\}}} \beta_{edu,mort} D_{edu} + X\gamma_{mort}\right)$$

Figure 3 compares $\beta_{low,BM}$, $\beta_{low,DD}$ and $\beta_{low,mort}$ for healthy, recent DD and older DD.

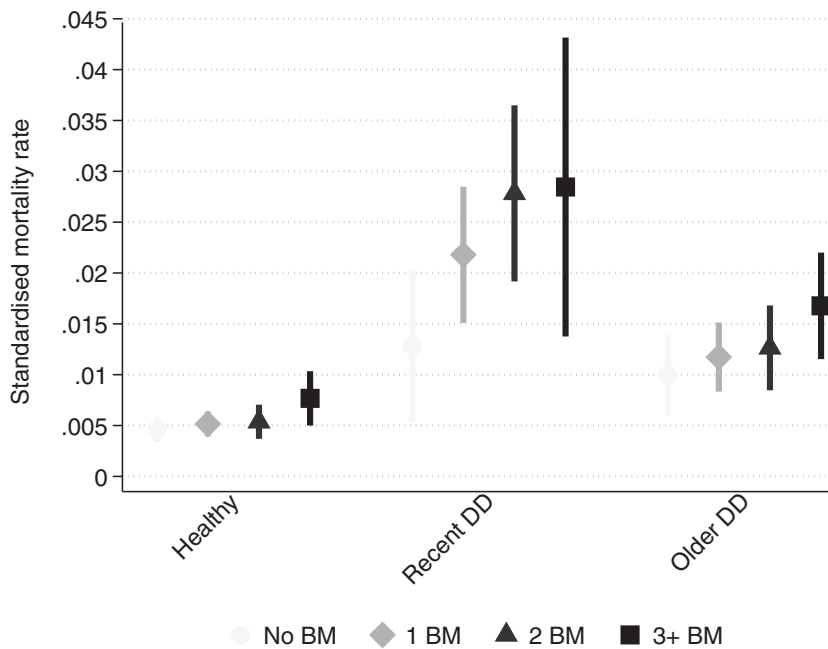
Appendix Table A1: Educational distribution, by gender, race and age

Gender	Race	Age	No high school, %	High school, %	College, %	Cell count
Men	White	51–59	8	28	64	1,211
		60–69	11	32	56	1,473
		70–79	20	36	43	1,435
		80–89	24	31	45	619
	Non-White	51–59	23	30	47	547
		60–69	31	30	39	349
		70–79	41	28	32	264
		80–89	55	19	26	80
Women	White	51–59	9	33	59	1,486
		60–69	13	38	48	2,040
		70–79	19	43	37	1,856
		80–89	22	43	35	837
	Non-White	51–59	22	28	50	781
		60–69	34	29	36	607
		70–79	43	31	26	404
		80–89	57	22	21	113

Figure A1: Rate ratios for educational groups (no high school vs some college) for biomarkers, doctors' diagnoses and mortality; among the healthy, recently diagnosed and older diagnoses, *controlled for medication*.

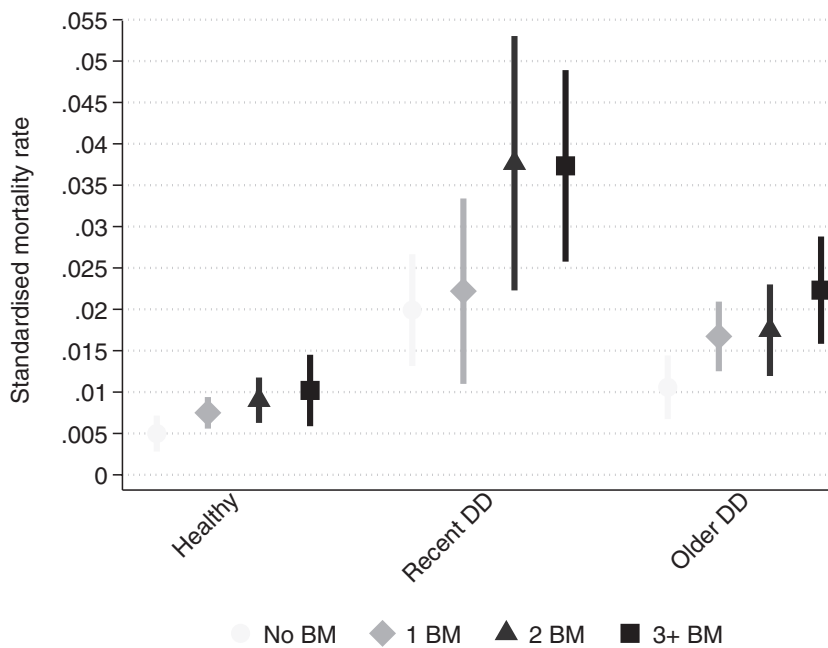
Notes: DD = diagnosis; BM = biomarker; The following items (measured at baseline) were used for constructing the variable medication, which is 1 if any of these are taken: blood pressure medication, heart medication, heart attack medication, angina medication, congestive heart failure medication, stroke medication.

Figure A2a: Standardised mortality rates for healthy individuals, the recently diagnosed and those with older diagnoses; with and without biomarkers, *men*.



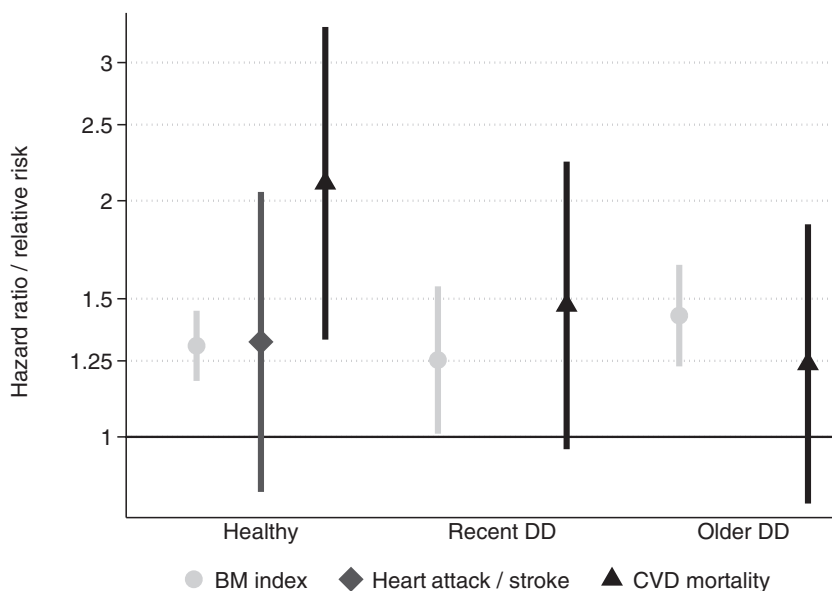
Notes: DD = diagnosis; BM = biomarker.

Figure A2b: Standardised mortality rates for healthy individuals, the recently diagnosed and those with older diagnoses; with and without biomarkers, *women*.



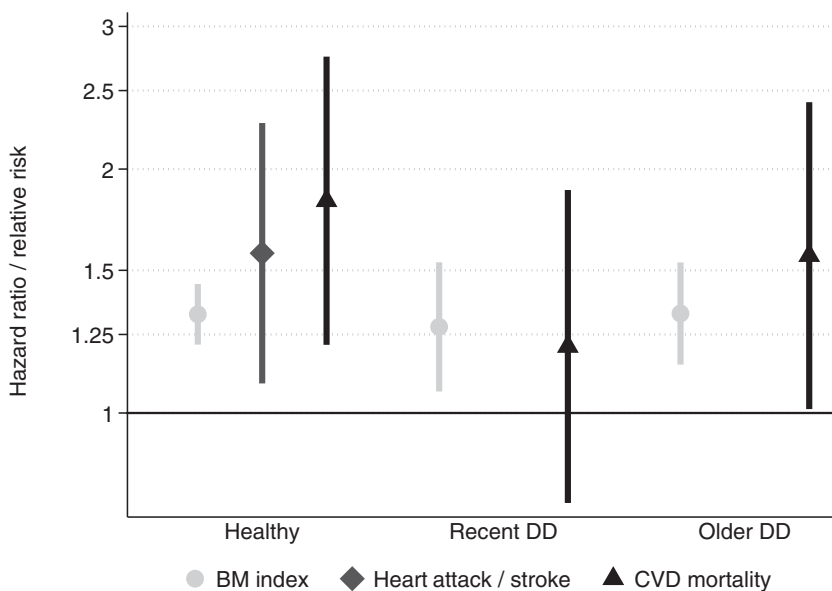
Notes: DD = diagnosis; BM = biomarker.

Figure A3a: Rate ratios for educational groups (no high school vs some college) for biomarkers, doctors' diagnoses and mortality; among the healthy, recently diagnosed and older diagnoses, *men*.



Notes: DD = diagnosis; BM = biomarker.

Figure A3b: Rate ratios for educational groups (no high school vs some college) for biomarkers, doctors' diagnoses and mortality; among the healthy, recently diagnosed and older diagnoses, *women*.



Notes: DD = diagnosis; BM = biomarker.