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Research Article

The association between CVD-related biomarkers and mortality in the Health and Retirement Survey

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Contents

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Abstract

BACKGROUND
It has become increasingly common in multiple purpose general population surveys to integrate different kinds of biomarker in the data collection process.

OBJECTIVE
In this article we test the predictive power of five different functional forms of CVD-related biomarkers for all-cause and CVD mortality in the Health and Retirement Study (HRS).

METHODS
We use five different functional forms of biomarker: A risk factor index, risk factors separately, continuous biomarkers, risk groups comprising every possible combination of risk factors, and a cluster analytic approach to identify risk profiles in the sample. We use data from the Health and Retirement Study (HRS) with information on four collected biomarkers (glycated hemoglobin (hbA1c), high-density lipoprotein (HDL), total cholesterol, and C-reactive protein (CRP)) with an eight-year mortality follow-up period.

RESULTS
The results show that the additive index has comparatively high predictive power, relative to its simplicity. Risk profiles were identified in the data, with substantial differences in mortality risk between the profiles. The more complex functional forms improve prediction only moderately compared to the simple index, although we can identify groups with an elevated mortality risk that are not identified in more parsimonious approaches.

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CONCLUSIONS
Depending on the specific research question, both a very simple modeling of biomarker information and more detailed examinations of specific complex risk profiles can be appropriate.

CONTRIBUTION
The study provides initial guidelines for the measurement of commonly used biomarkers, which can be a reference for other studies that use biomarkers as health indicators or for mortality prediction.

1. Introduction

It has become increasingly common in multiple purpose general population surveys to integrate different kinds of biomarker in the data collection process. This enables the objective measurement of different aspects of respondents' health status in addition to conventional self-reported measures (Layard 2010; Lindau and McDade 2008). This combination allows researchers to bridge disciplinary boundaries between social sciences, epidemiology, and medical and health sciences. The problem during data collection is one of limited resources, both in terms of the time and effort of the respondents themselves and with regard to the financial resources necessary to measure biomarkers (Hauser et al. 2010; Weir 2008). This limitation forces general population surveys – for which health is just one dimension among others – to focus on a reduced subset of potentially relevant biomarkers. Therefore, many surveys have primarily relied on biomarkers that have been shown in prior (clinical) research to be predictive of cardiovascular disease (CVD), as this constitutes the major cause of death in midlife and old age in most countries hosting these surveys (Hernon 2013; Lozano et al. 2012; Murray and Lopez 1997).

One challenge in the use of these biomarkers is how to integrate them into traditional survey-based research in the social sciences, public health, or social epidemiology. When biomarkers are supposed to complement or substitute self-reported indicators of health, the way in which they are used in the general population needs to be determined. Generally, there are two opposing approaches: On the one hand, a focus on very specific conditions like diabetes could warrant the use of one specific biomarker like hbA1c or C-reactive protein (CRP); for example, using hbA1c as a screening tool for undiagnosed diabetes (Bennett, Guo, and Dharmage 2007; Rohlfing et al. 2000), or investigating the relationship between CRP and depressive symptoms (Hamer and Chida 2009). On the other hand, research can focus more on the overall wear and tear of the body as represented by the concepts of allostatic load (Delpierre et

al. 2016a; Juster, McEwen, and Lupien 2010; McEwen 1998; Seeman et al. 2001) and biological age (Levine and Crimmins 2014), or on more specific CVD indices, including the well-known Framingham Heart Score (Lloyd-Jones et al. 2004). In many applications it is difficult to find an explicitly theoretically driven framework for the implementation of biomarkers in survey research. It is thus important to have external references upon which the decision of how to use biomarkers can be based. In this study we provide evidence of the association between mortality and a reduced set of CVD-related biomarkers, helping future studies to determine which functional form of biomarker might be most suitable for their approach.

Using binary risk factors is the most common approach to utilizing the information contained in biomarkers; this method is based on clinical evidence of the harmfulness of experiencing certain conditions above a certain threshold (e.g., hypertension if systolic blood pressure is elevated above 140 mmHg). Many biosocial surveys give explicit guidelines to users on how to construct such risk factors, which makes them easy to use even without prior experience in this field (Benzeval et al. 2014; Crimmins et al. 2013). Our analyses are therefore of an explanatory nature, and are designed to determine whether mortality prediction is best achieved by using a simple risk factor index, binary risk factors, continuous biomarkers, risk profiles, or risk groups based on a combination of risk factors.

The concept of risk profiles is based on the idea that a combination of certain values might be an important predictor of mortality, beyond the categorization into specific risk factors. Previous research has used partitioning methods (Gruenewald et al. 2006), configurative approaches based on risk factors (Shmotkin et al. 2010), and latent class analysis based on risk factors (Vasunilashorn et al. 2014) to determine specific groups of people that might have elevated mortality risks. We propose a risk profile approach that clusters levels of biomarkers not by their mortality risk (as with partitioning methods), nor by risk factors (like the latent class approach), but by continuous biomarkers, allowing for maximum flexibility when identifying groups of individuals in the data. We call the groups found through this cluster analytical approach 'risk profiles.' This method is agnostic as to whether biomarker profiles are predictive of mortality, a result that is implicit in the recursive partitioning approach. An additional benefit of such an analysis is that risk profiles might identify groups at risk that would not be captured by standard approaches. For example, it is conceivable that very high levels of one marker in combination with other elevated biomarkers might indicate multiple comorbidities whose combined risk exceeds the sum of the level of each biomarker. Another example might be the potentially harmful effects of very low levels of, for example, blood pressure (hypotension as opposed to hypertension) in conjunction with inflammatory processes. These lower levels could be identified in a risk profile, but not in a classical binary risk factor approach.

With our study we provide evidence that can guide the use of biomarkers in biosocial surveys and contribute to the literature examining different functional relationships between survey-based biomarkers and mortality.

The main criteria that we try to balance when comparing the different specifications of functional forms of biomarkers are the predictive power of the whole model and of group membership in identified risk groups on the one hand, versus the parsimony of the model specification on the other. Predictive power in our context means how well the model can distinguish between those who die and those who survive in the period of observation and how well the predicted age of death matches the observed age of death. Ultimately, a strongly predictive model is desirable, but the complexity of the model is a natural trade-off. A model can always be made more predictive by adding any number of variables to the model or by introducing interactions between existing variables. However, the more complex a model is, the harder it will be to interpret theoretically, and the greater the risk of overfitting. Overfitting means that the model produces good results in the data set being researched, but will perform relatively poorly when the model is applied to another dataset because the complexity of the model takes too many dataset-specific idiosyncrasies into account that do not reflect actual underlying processes in the population. Therefore, a reduction in complexity is also valuable – if it does not come at too great a cost of predictive power – because it allows future research to integrate simpler functional forms of biomarker into their studies more easily and to focus on other areas of the model.

2. Data and methods

We use data from the Health and Retirement Study (HRS), a survey of the general household population aged 50+ in the US (Sonnega et al. 2014). The HRS is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. In our analyses we use both the harmonized HRS data set from RAND[3] (RAND 2016) and sensitive health data on biomarkers (Health and Retirement Study 2013).

In the HRS, blood-based, CVD-related biomarkers were collected in 2006 for one half of the total sample and in 2008 for the other half. HRS uses the dried blood spot method to collect biomarkers (Crimmins et al. 2014). We use the first measurements of blood spots in HRS (2006 and 2008) and an eight-year mortality follow-up to assess all-cause mortality (six-year follow up for those who had their blood spots taken in 2008).

[3] The RAND HRS data file is an easy-to-use longitudinal data set based on the HRS data. It was developed at RAND with funding from the National Institute on Aging and the Social Security Administration.

The analyses exclude individuals with invalid survey weights or missing information on the race control variable, those who have information missing entirely on three or more of the four biomarkers given below (or on the death indicator), and those who are never observed beyond the first time point of measurement (1,350 cases). Those with partially missing data on biomarkers are retained; multiple imputation by chained equation (MICE) is used to handle the missing data (White, Royston, and Wood 2011). Thirty imputed data sets are used for the analyses, and the parameters and standard errors are calculated by applying Rubin's rule (Rubin 2004). This leaves 14,416 individuals to be analyzed, of whom 2,029 die during the period of observation, 794 of them with CVD as the main cause of death.

We study four biomarkers in this study: cholesterol, hbA1c, C-reactive protein, and systolic blood pressure. In the sample the correlation between systolic and diastolic blood pressure is over 0.7, indicating that they transport similar information. We use the ratio of total cholesterol to HDL cholesterol, as the first waves of data collection in HRS using the dried blood spot method resulted in implausible cholesterol levels. Although all measures in HRS were adjusted to reflect levels equivalent to markers taken from venous blood (Crimmins et al. 2014), the levels of total and HDL cholesterol deviate strongly from those in reference studies like NHANES (Crimmins et al. 2013). The distortion is proportional for total and HDL cholesterol, so that the ratio is comparable to other studies. It holds for all four biomarkers that we study that higher values potentially indicate more problems. However, there are cut-off values that have been used previously in the literature which indicate that the biomarker lies outside the normal range and a potential health risk is present. The cut-off points used to define binary risk factors from the continuous measures of the biomarkers are noted in parentheses:

1. Ratio of total to HDL cholesterol (Men: ≥ 5; Women: ≥ 4.5)
2. Glycated hemoglobin, hbA1c ($\geq 6.4\%$)
3. C-reactive protein ($\geq 3 \frac{mg}{l}$)
4. Systolic blood pressure (SBP, $\geq$140 mmHg)

The chosen cut-off for cholesterol is a little lower than in previous studies (Rosero-Bixby and Dow 2009; Seeman et al. 2004), to be sure to also include those with some degree of measurement error in the risk group. The cut-off for hbA1c conforms to both a common recommendation (American Diabetes Association 2011; World Health Organization 2011) and to previous studies (Delpierre et al. 2016b; Goldman et al. 2011; Rosero-Bixby and Dow 2009). The CRP cut-off has also been used in previous studies (Crimmins et al. 2013, 2014; Osman et al. 2006) and follows standard recommendations (Pearson et al. 2003). The systolic blood pressure cut-off has been

used in previous studies (Rosero-Bixby and Dow 2009; Seeman et al. 2004) and has been tested in a randomized control trial (The SPRINT Research Group 2015).

All analyses are weighted by weights provided by the HRS survey team (Crimmins et al. 2013). These weights are meant to account for non-random sampling and selective non-response to participation in the biomarker measurement. Table 1 presents the summary statistics in the sample. All data preparation and analyses use Stata 14.2 including user-written packages (Jann 2007). The calculation of the area under the curve (AUC) for the survival analytic models was done in R 3.4.1 using the survivalROC package (Heagerty and Saha-Chaudhuri 2013).

Table 1: Summary statistics

	Mean	SD	Minimum	Maximum	Missing
Age at measurement	67.11	9.69	51.00	89.00	0
White	0.78	0.42	0.00	1.00	0
Black	0.16	0.37	0.00	1.00	0
Other	0.06	0.24	0.00	1.00	0
Male	0.43	0.49	0.00	1.00	0
Risk factors					
High ratio of TC to HDL (>5)	0.22	0.42	0.00	1.00	2,126
High hbA1c (≥6.4%)	0.16	0.37	0.00	1.00	159
High CRP (≥3.0 ug/mL)	0.38	0.49	0.00	1.00	520
High risk systolic BP (≥140 mmHG)	0.32	0.47	0.00	1.00	694
Continuous biomarkers					
Ratio of TC to HDL	3.97	1.24	1.33	23.85	2,126
Blood glycated hemoglobin level (%)	5.89	1.04	3.57	17.26	159
Blood CRP level (ug/mL)	4.36	8.31	0.02	280.00	520
Systolic BP (mmHG)	131.62	20.35	41.67	223.33	694
Observations	14,416				

In our study we consider five different functional forms of the biomarker data that is collected in HRS. First, we compose a simple index ("index") counting the number of risk factors individuals exhibit, which ranges from 0 to 4. Second, we consider the risk factors as separate dichotomous indicators, which is the most common approach ("risk factors"). Third, we use the biomarkers in their continuous form ("continuous"). Fourth, we define risk groups based on every possible combination of risk factors, resulting in 2^4=16 risk groups ("risk groups," RG). Fifth, we use a cluster analytic approach to identify risk profiles based on the continuous information from the biomarkers ("risk profiles," RP).

These different ways of transforming the information contained in the original biomarker measurements are reflective of the different degrees of complexity and specificity with which biomarker information can be used.

3. Analyses

We assess the predictive power of the different functional forms of biomarker in two ways. First, we look for differences in mortality risk between risk groups based on biomarkers using Cox proportional hazard models. Second, we evaluate the overall model fit by employing a classification measure, namely the area under the curve (AUC) based on the receiver operating characteristic (ROC), developed for survival analytic models (Heagerty and Zheng 2005). All models are adjusted for a second order polynomial of age at the time of blood spot measurement, a dummy for white versus non-white, and gender.

Before the analyses of predictive power can be conducted, we require a cluster solution to identify biomarker risk profiles in the data. We perform a cluster analysis using the method of Ward and Hook (Ward 1963; Ward and Hook 1963) and Euclidean distance as the dissimilarity measure. All biomarkers are z-standardized to enable the equal contribution of each biomarker to the cluster solution, despite differences in scaling. In finding an optimal cluster solution we aim to balance a parsimonious approach, with the goal of identifying hidden combinations of biomarker levels that might be harmful. To retain a level of parsimony, the maximum number of clusters should not exceed the number of risk groups derived from the combination of risk factors, which is 16. Given a maximum number of 16 clusters, we use the elbow criterion on two scree plots to determine the number of clusters. We look at the increase in the dissimilarity, which is the traditional criterion endogenous to the clustering algorithm, but more importantly we look at the decrease in predictive power in terms of the AUC with each step of merging two clusters. We choose the solution of 16 clusters or fewer for which we find the first significant decrease in AUC or significant increase in the dissimilarity measure, whichever comes first.

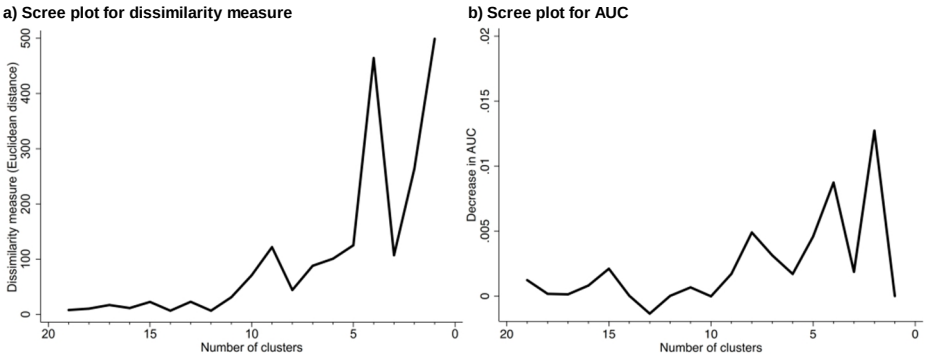
4. Results

4.1 Cluster solution

Figures 1a and 1b show the scree plot for the dissimilarity measure and the AUC respectively. For the dissimilarity measure, the first strong increase is from an 11 to a 10 cluster solution, and then, even stronger, from a 10 to a 9 cluster solution. For the AUC we can see that there are two spikes indicating a decrease in AUC with 16 clusters or fewer. One is from 16 to 15 clusters and the other from 9 to 8 clusters. The second decrease is stronger, and we choose this solution to further reduce the level of

complexity in the analyses, resulting in a 9-cluster solution instead of a 16-cluster solution.

Figure 1: Scree plot



Note: The figure shows the relationship between the cluster solution and the dissimilarity measure (left panel 1a) and the decrease in AUC in a survival analytic model (right panel 1b).

4.2 Description of risk groups and risk profiles

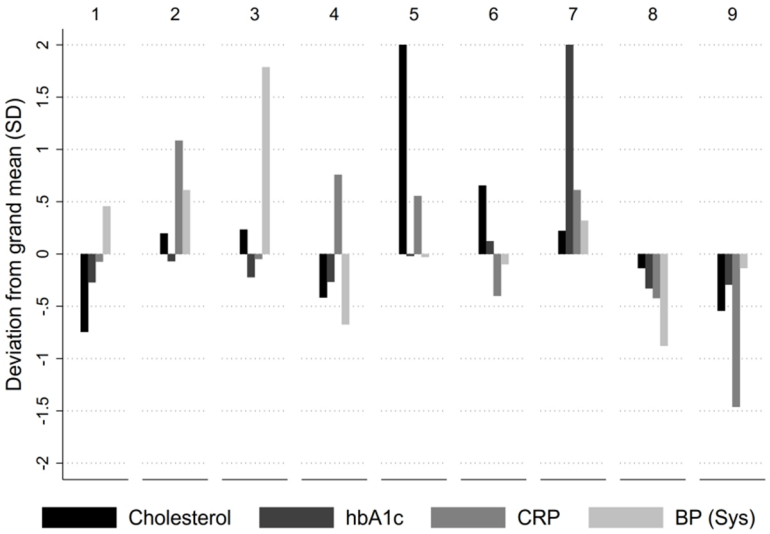
We classify individuals into complex risk groups in two ways. First, we define each combination of the four risk factors as a separate group, with those who have no risk factor as the reference (0000). In this way we can distinguish, for example, those with high inflammation (0010) and no other risk factor from those with high cholesterol ratio and high blood pressure (1001), or those with all four risk factors present (1111). Table 2 gives an overview of all the groups and their distribution. Second, we apply an explanatory approach to establish risk profiles using cluster analysis on standardized continuous biomarker measures. As described above, we consider a 9-cluster solution to represent the optimal trade-off between the explanatory power for mortality and the parsimony of the functional form of the biomarkers.

Table 2: Risk groups as combinations of risk factors and their distribution in the sample

	Risk factor					
Risk group	Cholesterol	hbA1c	CRP	BP(sys)	N	Prop. (%)
0000	0	0	0	0	3,624	31.05
0001	0	0	0	1	1,492	12.78
0010	0	0	1	0	1,809	15.5
0011	0	0	1	1	844	7.23
0100	0	1	0	0	453	3.88
0101	0	1	0	1	282	2.42
0110	0	1	1	0	373	3.2
0111	0	1	1	1	227	1.94
1000	1	0	0	0	814	6.97
1001	1	0	0	1	331	2.84
1010	1	0	1	0	594	5.09
1011	1	0	1	1	334	2.86
1100	1	1	0	0	124	1.06
1101	1	1	0	1	90	.77
1110	1	1	1	0	150	1.29
1111	1	1	1	1	130	1.11

Figure 2 describes the risk profiles – the result of our preferred cluster solution – in terms of their deviation from the grand mean of the z-standardized biomarker values. Risk profile 1 (RP1) shows elevated levels of blood pressure, but is slightly lower than average for the other biomarkers. RP2 is a profile with low cholesterol but high inflammation and very high blood pressure. RP3 displays high CRP levels and low blood pressure levels. RP4 has very high CRP levels and average levels for the other biomarkers. RP5 has an extremely high level of cholesterol and slightly elevated CRP and blood pressure. RP6 shows extremely high values for hbA1c, also indicating (hidden) diabetes, but increased levels for all other biomarkers as well. RP7 has increased hbA1c, indicating hidden diabetes, but only average levels of other biomarkers. RP8 is an overall low-risk profile with particularly low cholesterol and blood pressure levels. RP9 is another low-risk profile, with particularly low levels of CRP and blood pressure.

Figure 2: Description of cluster solution in standard deviations from the sample mean



Note: Cholesterol = Ratio of total to HDL cholesterol; hbA1c = Glycated hemoglobin; CRP= C-reactive protein; BP (SYS) = Systolic blood pressure

4.3 Mortality prediction of different functional forms

Table 3 shows the results from Cox proportional hazard models on the five different ways of coding the four biomarkers. The simplest form is an index counting the number of risk factors. It shows that the more risk factors an individual has, the higher their predicted mortality risk. Individuals with four risk factors have a mortality risk as much as 3.54 times higher (CI: 2.41; 5.21) than that of those without any risk factors. The second method, also fairly traditional, is to introduce each risk factor separately, showing that CRP (HR 1.77 [CI: 1.59; 1.96]) and hbA1c (HR 1.58 [CI: 1.40; 1.78]) is especially predictive of mortality. The risk factors for cholesterol and blood pressure do not significantly increase the mortality risk. Taking the continuous values of the biomarkers in continuous form yields similar results, with CRP and hbA1c being predictive while the others are not.

Table 3: Hazard ratios from Cox models on all-cause mortality with different functional forms on their own

	(1)		(2)		(3)		(4)		(5)	
Male	Ref.		Ref.		Ref.		Ref.		Ref.	
Female	0.66	[0.60,0.73]	0.64	[0.58,0.70]	0.67	[0.61,0.74]	0.64	[0.58,0.71]	0.63	[0.57,0.70]
White	Ref.		Ref.		Ref.		Ref.		Ref.	
Black	1.24	[1.06,1.44]	1.18	[1.01,1.37]	1.21	[1.03,1.41]	1.22	[1.05,1.43]	1.18	[1.01,1.37]
Other	0.82	[0.62,1.10]	0.82	[0.61,1.10]	0.78	[0.58,1.05]	0.82	[0.61,1.10]	0.82	[0.61,1.09]
Age at measurement	1.00	[0.80,1.25]	0.99	[0.79,1.24]	1.01	[0.81,1.26]	1.01	[0.81,1.27]	0.99	[0.79,1.24]
Age^2	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
Number of risk factors										
0	Ref.									
1	1.43	[1.24,1.66]								
2	1.70	[1.45,1.98]								
3	2.20	[1.80,2.68]								
4	3.54	[2.41,5.21]								
Risk factors										
High ratio of TC to HDL (>5)			1.00	[0.88,1.14]						
High hbA1c (≥6.4%)			1.58	[1.40,1.78]						
High CRP (≥3.0 ug/mL)			1.77	[1.59,1.96]						
High risk systolic BP (>139)			1.00	[0.90,1.12]						
Continuous biomarkers										
Ratio of TC to HDL					1.04	[1.00,1.08]				
Blood glycated hemoglobin level					1.18	[1.13,1.23]				
Blood CRP level					1.01	[1.01,1.02]				
Systolic BP					1.00	[1.00,1.00]				
Risk profiles										
1							Ref.			
2							1.93	[1.55,2.39]		
3							1.31	[1.04,1.64]		
4							1.76	[1.43,2.18]		
5							1.64	[1.24,2.16]		
6							1.01	[0.80,1.27]		
7							3.10	[2.42,3.96]		
8							1.09	[0.87,1.38]		
9							0.86	[0.67,1.09]		
Risk groups										
0000									Ref.	
0001									1.15	[0.95,1.40]
0010									1.95	[1.64,2.33]
0011									1.58	[1.27,1.96]
0100									1.48	[1.13,1.95]
0101									1.63	[1.21,2.20]
0110									3.18	[2.42,4.19]
0111									2.68	[2.03,3.55]
1000									1.03	[0.78,1.37]
1001									1.02	[0.72,1.45]
1010									1.82	[1.40,2.37]
1011									1.76	[1.33,2.35]
1100									1.36	[0.88,2.10]
1101									2.07	[1.26,3.37]
1110									2.69	[1.76,4.11]
1111									3.57	[2.43,5.26]
N	14,416		14,416		14,416		14,416		14,416	
AUC	0.599		0.615		0.596		0.618		0.617	

Model 4 shows mortality risk differences between the RPs identified in the data. With reference to RP1 (slightly higher BP, low other markers), only RP6 (very high hBA1c, elevated other biomarkers), RP8, and RP9 (the low risk profiles) do not differ significantly in terms of mortality risk. The mortality risk increases considerably for RP7 (high hbA1c, average other biomarkers HR 3.10 [CI: 2.42; 3.96]), and moderately for RP2 (low cholesterol, but high BP and CRP, HR 1.93 [CI: 1.55; 2.39]) and RP4 (very high CRP, HR 1.76 [CI: 1.43; 2.18]). The other profiles show even lower HR. This shows that high inflammation and undiagnosed (or untreated) diabetes are strong risk factors, as is high cholesterol. A surprising result is that RP6, which has extremely high levels of hbA1c and increased other biomarkers, is not associated with increased mortality risk, even though one would expect it to be, given the diabetes risk and increased other biomarkers.

Using the combination of predefined risk factors as risk groups, we see some of these results validated. Unsurprisingly, the highest mortality risk is for those who have all four risk factors. Also particularly high are those with both CRP and hbA1c (0110, HR 3.18 [CI: 2.42; 4.19]), those with all risk factors present except elevated blood pressure (1110, HR 2.69 [CI: 1.76; 4.11]), and those with all risk factors present except high cholesterol (0111, HR 2.68 [CI: 2.03; 3.55]).

It is of further interest to establish which of the functional forms retain predictive power if the other functional forms are controlled for. For this purpose we estimated three further models, which are composed of, respectively:

a) the index, the continuous data, and the risk profiles (RPs);
b) the risk factors (RFs), the continuous data, and the RPs, and
c) the continuous data, the RPs, and the risk groups.

The risk groups, risk factors, and the index cannot be tested in one model, because the risk groups are completely linear combinations of the risk factors and the index is a partially linear combination of the risk factors, and therefore completely or partially collinear. If the risk group is known, by definition the exact combination of risk factors is also known (see Table 2). Therefore, the risk groups carry all information of the risk factors plus their interaction. Consequently, their effects cannot be estimated separately in the same model, because the risk groups completely contain the information of the risk factors. The risk index is partially collinear with the risk groups and risk factors. If the index is zero, we know that each risk factor is zero and the risk group is 0000. If the risk index is 4, we know that each risk factor must be 1 and the risk group is 1111. Therefore, we cannot estimate the coefficients for the levels of the index in the same model as the risk groups or the risk factors.

When taking the RPs and continuous levels into account, the index still retains some predictive power, with those who have 3 or 4 RFs showing an increased mortality risk (HR 1.62 [CI: 1.20; 2.18] and 2.37 [CI: 1.48; 3.79] respectively). The mortality risk differences for the RPs are somewhat attenuated in all three models, but especially the RPs mentioned above (2,4,7) still show substantially higher mortality risk, even when taking risk factors, continuous measures, and even the predefined risk group combinations into account. For continuous biomarkers, only CRP retains some predictive power; however, its effect is smaller than the unconditional effect estimate, albeit still significant in all three models.

For the risk factors the hazard ratios of CRP and hbA1c are also attenuated, but exhibit some increased mortality risk when taking RPs and continuous measures into account (HR 1.31 [CI: 1.12; 1.53] and 1.42 [CI: 1.19; 1.69] respectively). Finally, the risk groups are also attenuated; when controlling for RPs and continuous measures, however, the same combinations as above show an increased mortality to a greater extent than RP membership.

Figures 3 and 4 plot the AUC for the survival models. The left-hand panel shows the results for all-cause mortality, the right-hand panel the results for CVD mortality. We will first discuss the results for all-cause mortality and then turn to the results for CVD mortality in a separate section. Within the panels the results are divided into analyses for the total sample and into analyses for gender- and age-specific subgroups. Again, we will first discuss the results for the total sample and turn to the subgroup-specific results in a separate section.

The AUC can be interpreted as the predictive power that an individual will be correctly classified as being dead or alive at a given age, but averaged over age to simplify the results; predictive power does not change substantially with age (see Figure A-1 in Appendix). The different bars indicate the five different functional forms. The figure only plots the increase in AUC above the initial predictive power of the baseline model. The absolute AUC is reported in the complete model output (Tables 3 and 4, as well as Appendix A-2.1–A-2.20 and A-3.1–A-3.20), and as an overview in Table A-1 in the Appendix. We distinguish between the gross increase in predictive power of a functional form (Figure 3) and its marginal increase in predictive power (Figure 4). The former refers to the increase in AUC over the baseline model when entering a functional form on its own. The latter is a calculation of how much the AUC is increased if other functional forms are already included and the respective functional form is added to the model. The marginal increase will, by definition, always be lower than the gross increase.

Table 4: Hazard ratios from Cox models on all-cause mortality with different functional forms conditional on the other forms

	(1)		(2)		(3)	
Male	Ref.		Ref.		Ref.	
Female	0.63	[0.57,0.70]	0.64	[0.58,0.72]	0.64	[0.58,0.71]
White	Ref.		Ref.		Ref.	
Black	1.17	[1.00,1.37]	1.16	[0.99,1.35]	1.16	[0.99,1.36]
Other	0.81	[0.60,1.08]	0.81	[0.60,1.08]	0.81	[0.60,1.08]
Age at measurement	1.01	[0.81,1.26]	1.00	[0.80,1.25]	1.00	[0.80,1.25]
Age^2	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
Number of risk factors						
0	Ref.					
1	1.32	[1.09,1.59]				
2	1.38	[1.10,1.73]				
3	1.62	[1.20,2.18]				
4	2.37	[1.48,3.79]				
Risk factors						
High ratio of TC to HDL (>5)			0.92	[0.75,1.13]		
High hbA1c (≥6.4%)			1.42	[1.19,1.69]		
High CRP (≥3.0 ug/mL)			1.31	[1.12,1.53]		
High risk systolic BP (>139)			1.02	[0.85,1.22]		
Continuous biomarkers						
Ratio of TC to HDL	0.98	[0.92,1.04]	1.05	[0.97,1.13]	1.05	[0.97,1.13]
Blood glycated hemoglobin level	1.05	[0.98,1.13]	1.01	[0.93,1.10]	1.01	[0.93,1.10]
Blood CRP level	1.01	[1.00,1.01]	1.01	[1.00,1.01]	1.01	[1.00,1.01]
Systolic BP	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	1.55	[1.21,1.99]	1.38	[1.07,1.79]	1.47	[1.12,1.92]
3	1.28	[0.98,1.68]	1.25	[0.95,1.63]	1.26	[0.96,1.65]
4	1.54	[1.22,1.95]	1.42	[1.10,1.83]	1.40	[1.07,1.83]
5	1.39	[0.97,1.98]	1.21	[0.83,1.76]	1.23	[0.84,1.81]
6	0.95	[0.74,1.23]	0.90	[0.69,1.17]	0.93	[0.70,1.22]
7	2.05	[1.43,2.95]	1.77	[1.23,2.53]	1.79	[1.23,2.60]
8	1.19	[0.90,1.56]	1.12	[0.86,1.45]	1.17	[0.89,1.55]
9	0.92	[0.72,1.19]	0.91	[0.71,1.17]	0.92	[0.72,1.19]
Risk groups						
0000					Ref.	
0001					1.19	[0.92,1.52]
0010					1.46	[1.15,1.85]
0011					1.23	[0.92,1.66]
0100					1.46	[1.05,2.01]
0101					1.47	[1.03,2.12]
0110					2.05	[1.46,2.88]
0111					1.80	[1.25,2.58]
1000					0.99	[0.70,1.40]
1001					0.88	[0.56,1.38]
1010					1.28	[0.90,1.82]
1011					1.22	[0.84,1.77]
1100					1.14	[0.69,1.88]
1101					1.57	[0.89,2.76]
1110					1.74	[1.05,2.87]
1111					2.21	[1.37,3.55]
N	14,416		14,416		14,416	
AUC	0.625		0.625		0.626	

Note: 95%-CI in brackets.

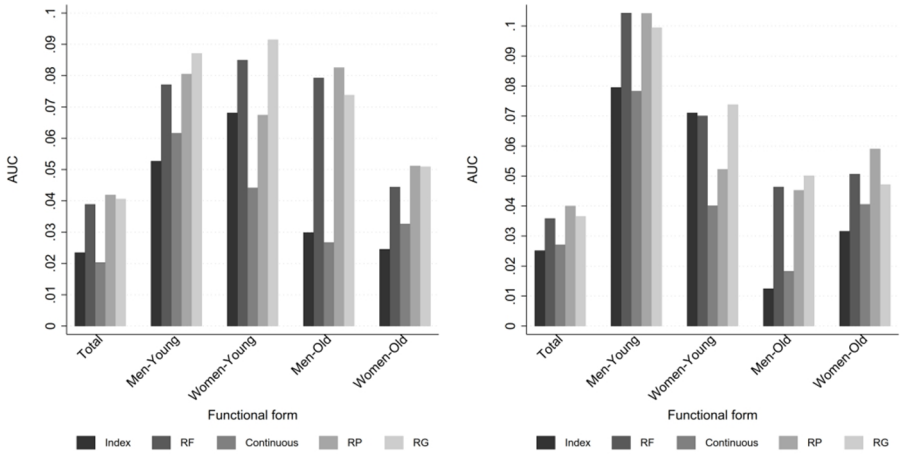
We can see in Figure 3 that continuous biomarkers have the lowest gross increase in AUC (0.02), meaning comparatively low predictive power for mortality status. The risk index is the second lowest (0.024); after that, the risk factors, risk groups, and risk profiles have higher gross AUC, and are very close together (about 0.04). Overall, the gross increase in predictive power is not very high, with an increase from 0.576 to a maximum of 0.618.

The marginal gains shown in Figure 4 are, of course, smaller than the gross gains. The continuous biomarkers are lowest again, and risk profiles and risk groups have the highest marginal discriminatory power, but the additional gain remains below 0.01 in all cases.

Summing up, we can say that the different functional forms of the four biomarkers under study show some degree of gross and marginal predictive power. We established that especially those groups with extreme values in CRP (RP4), hbA1c (RP7), and blood pressure (combined with increased CRP, RP2) have an increased mortality risk, even accounting for their specific risk factor combinations. Extreme values of CRP are often taken as indicators of acute rather than chronic inflammation, and previously have often been excluded when taking CRP as an indicator of chronic inflammation (Osman et al. 2006). These results show that very high levels of CRP actually do correlate with an additional increase in mortality risk, and thus that it might only be prudent to exclude them if one wants to target just chronic conditions and can also be sure that such elevated levels are due solely to inflammatory diseases, which is not always the case (Ishii et al. 2012). The risk groups showed that the combination of CRP and hbA1c is particularly associated with elevated mortality, and also that merely a higher number of risk factors, regardless of the specific combination, increases the mortality risk – highlighting the validity of the simple risk factor index.

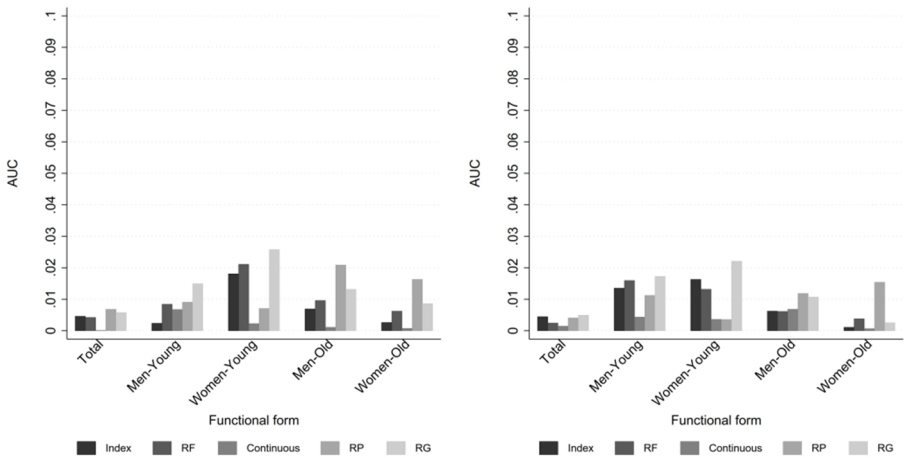
The analyses of the discriminatory power of the model in the form of the AUC highlighted three facts. First, overall predictive power is low, which is to be expected when taking only four CVD-related biomarkers into account. Second, the more complex risk groups and risk profiles have higher classificatory power than the index or the risk factors alone. Third, the cumulative gain of more complex functional forms over the simple index is measurable but relatively small compared to the overall level of the AUC, yielding a little less than 0.01 in terms of the AUC.

Figure 3: Gross increase in Area under the Curve (AUC) for each functional form separately and by subgroup



Note: The AUC is averaged over age in the total sample and within the age-specific groups. The left hand panel shows all-cause mortality, the right hand panel CVD mortality. RF = risk factors; RP = risk profiles; RG = risk groups.

Figure 4: Marginal increase in Area under the Curve (AUC) for each functional form separately and by subgroup



Note: The AUC is averaged over age in the total sample and within the age-specific groups. The left hand panel shows all-cause, the right hand panel CVD-mortality. RF = risk factors; RP = risk profiles; RG = risk groups.

4.4 Cardiovascular mortality

As the four biomarkers used in this study are particularly indicative of cardiovascular-related diseases, we repeat the analyses using CVD-specific mortality instead of all-cause mortality as the event in the survival analytical models. The right hand panels of Figures 3 and 4 show that, for the total sample, levels of predictive power are about the same in CVD-specific and all-cause mortality models. The performance of continuous biomarkers is a little better in CVD-specific models relative to the other functional forms.

4.5 Gender- and age-specific results

We further explore whether the predictive power is different between the young (50–69) and old (70–89), with age referring to starting age, and whether the results differ between men and women. We divide the subgroups by age and gender simultaneously because the majority of deaths in young age are men, so that a division by age would be automatically correlated with gender in the results. For simplicity, we look just at the AUC for overall model predictive power. The results are reported in Figures 3 and 4. The gross predictive power of all functional forms is highest among young men, especially for CVD-specific mortality. For marginal predictive power the differences are smaller, and differences between groups are less pronounced. In old age, on average the biomarkers can predict mortality to a lesser degree, a result mainly driven by the poor performance of the index and continuous biomarkers. This indicates that in old age, more complex combinations might be necessary to adequately predict mortality, whereas the loss resulting from more parsimonious functional forms is lower in younger age groups.

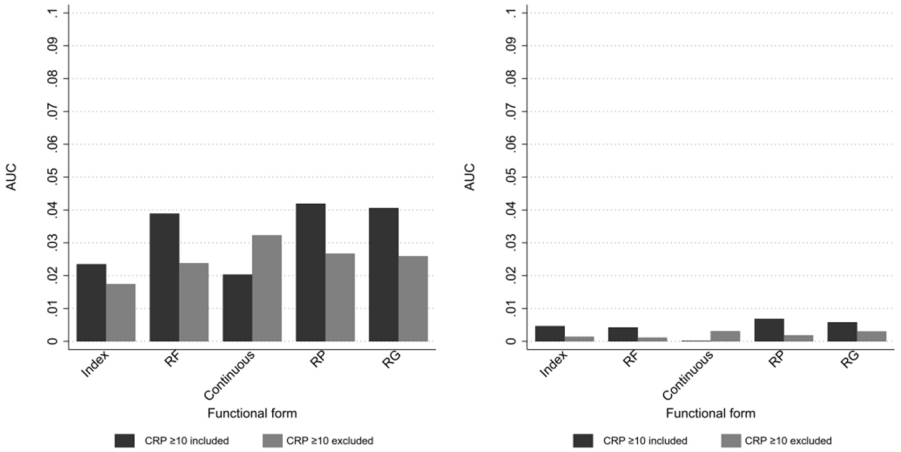
In almost all subgroups the continuous biomarkers perform worst, followed by the index. Risk groups, risk profiles, and risk factors consistently score higher in the AUC both in gross and marginal predictive power. However, among the three there is no clear trend indicating which one is best across subsamples. As the subgroups are more homogeneous with respect to mortality risk than the total sample, it comes as no surprise that the overall level of gross increase in predictive power within the subgroups is higher than in the total sample, regardless of functional form.

4.6 Excluding high levels of CRP

High levels of CRP (above $10\frac{\text{mg}}{\text{l}}$) are often seen as an indicator of acute illness, and some studies that focus on CRP as an indicator of chronic stress or allostatic load exclude those observations (Freeman et al. 2016). To check the sensitivity of our results to the decision to include or exclude individuals with very high CRP levels, we repeat all analyses for a sample restricted to CRP levels of below $10\frac{\text{mg}}{\text{l}}$ (1,809 individuals, 12.55% of the sample).

Figure 5 shows the comparison of the AUC with and without individuals with very high levels of CRP. The values chosen are for the total sample and all-cause mortality, but are illustrative of the structure in all model specifications (see Table A-1 in the Appendix). The most striking finding is that the continuous biomarkers gain in gross predictive power, while all other functional forms lose power. Excluding high-level CRP individuals leaves all four more complex functional forms with about the same level of predictive power, while the index is still lower. Looking at the marginal benefit on the right hand side of Figure 5, continuous biomarkers gain as well, but remain below the other functional forms.

Figure 5: Gross and marginal increase in Area under the Curve (AUC) by CRP-based exclusion criterion



Note: Numbers only for the total sample and all-cause mortality. Left hand panel shows gross increase, right hand panel the marginal increase in AUC. RF = risk factors; RP = risk profiles; RG = risk groups.

Thus, which population is under investigation in a study on CVD-related biomarkers, be it the whole population or only individuals with non-acute health problems, may also be potentially significant. The continuous biomarkers, especially CRP, have a much higher discriminatory power relatively and absolutely speaking when individuals suspected to have some kind of acute illnesses are excluded. This needs to be taken into account when making decisions about the functional form to be used; however, it should be noted that there is no correct choice per se, and the definition of the population to be examined depends on the specific research question.

5. Discussion

The aim of our study is to determine how a reduced set of CVD-related biomarkers, gathered as part of a population-based survey, is related to all-cause and CVD-related mortality. In particular, we try to estimate how much predictive power can be delivered by different functions – both parsimonious and more complex – of four biomarkers, as collected in the Health and Retirement Study (HRS). Simple codings – like an index, or the risk factors on their own – showed substantial risk differences and had adequate discriminatory power overall. Beyond these simple codings, certain combinations of risk factors, especially inflammation and diabetes biomarkers, identified groups of individuals at an increased risk of mortality. Using continuous biomarkers yielded the lowest overall predictive power in the total sample and contributed little additional predictive power, but had equal predictive power in a sample excluding individuals with very high levels of CRP (suspected acute illness). This highlights the fact that there is probably no universally valid optimal functional form: Different populations under study might warrant a different treatment of the biomarkers. Linearity seems to be violated in the case of CRP, and we can consider very high levels of CRP to have a different gradient than moderate levels (below 10 $\frac{\text{mg}}{\text{l}}$).

Within the sample we were also able to identify risk profiles that showed considerable differences in mortality risk, even after controlling for risk-factor-based functional forms of the biomarkers. Here, extreme values of CRP (in particular) and hbA1c were predictive, as was the combination of high CRP and very high blood pressure, beyond the simple fact of an individual possessing the risk factor or not.

This shows that not only a combinatory approach – as applied by Shmotkin et al. (2010) – but also an explanatory approach – as used here – can identify groups that carry an extra health risk and that would not be identified with the simpler risk-factor-based approaches. However, while the simplest form, the risk index, showed lower discriminatory power than the more complex functional forms, the results indicate that while there are some gains from choosing a functional form that is more complex than

the simple index, the total gain is modest. Therefore, we argue that in certain circumstances in which survey-based research focuses on generalized concepts like allostatic load (Delpierre et al. 2016a; Juster, McEwen, and Lupien 2010; McEwen 1998; Seeman et al. 2001), our results validate such a parsimonious approach, at least for the set of CVD-related biomarkers under study here. A similar approach might seem appropriate if health inequalities with respect to objective indicators are the subject of investigation (Dowd and Zajacova 2010; Rosero-Bixby and Dow 2009), as an alternative to looking at risk differences for specific health issues, such as hbA1c for diabetes (Bennett, Guo, and Dharmage 2007; Rohlfing et al. 2000).

On the other hand, a closer examination of groups that exhibit unusual combinations of biomarker levels might also be a worthwhile research undertaking, be it to establish the consequences of belonging to these risk groups or risk profiles, or to establish the determinants of being in such a risk group. The fact that the predictive power of several of the risk profiles was still present when taking other functional forms into account corroborates the interpretation that the combinations of biomarker levels are related to processes that affect the cardiovascular system (and perhaps other systems) beyond what we can diagnose from the simple risk factor approaches.

From the analyses of subgroups we were able to establish that gross increase in predictive power was higher for younger than for older individuals. In older age, many more factors come into play that contribute to mortality risk, reducing the overall discriminatory power of the biomarkers, regardless of functional form. We find no stronger link across all groups between the biomarkers and CVD mortality than is the case with all-cause mortality, despite the fact that the biomarkers under study are particularly predictive of CVD mortality. However, this refers to overall model prediction.

Limitations

Our study is limited in several ways. First, we only assess four biomarkers and their functional forms. The main reason here is data availability and comparability. HRS collects only a narrow range of biomarkers from dried blood spots and some additional measures like blood pressure. We further limited ourselves to measures that are also collected in other general population surveys internationally, to enable the comparability of the findings in this study with results from surveys of similar structure. This limits the conclusions we can draw, but our results suggest that simple functional forms could also have high predictive power in other areas; e.g., biomarkers of physical capabilities like grip strength, walking speed, or peak flow measures, which are also

used as indicators of frailty (Walston et al. 2006). Whether this hypothesis holds has to be tested in future studies.

Second, we excluded by design individuals who had all missing information on biomarkers and those who refused the biomarker collection. Although we used weights to account for selective participation in the blood spot measurements, it is possible that the results might be systematically different for certain individuals, perhaps those who were very infirm and at high mortality risk due to poor health at the time of the interview, thus resulting in their nonparticipation. Unfortunately, it is unclear whether this exclusion leads to an overestimation or underestimation of the predictive power of the functional forms of biomarkers we tested.

Third, we only investigated the biomarkers' relationship with all-cause and CVD-specific mortality. However, it would be interesting to establish the relationship with other cause-specific mortality. Despite the fact that the biomarkers investigated in HRS were collected with a special focus on cardiovascular disease (Weir 2008), the results for all-cause mortality are similar to those for CVD mortality with respect to predictive power. Nevertheless, for more specific analyses, a dataset with a higher number of events and a more specific classification of causes of deaths is needed in future research.

Finally, we only evaluated one survey; it is important to replicate the analyses using different data sets, as our strategy was largely explorative. When testing the approach with other data, it would be productive both to analyze a data set that had no or little prior panel attrition – as the HRS has (Domingue et al. 2017) – and also to use data in which biomarkers were collected not from dried blood spots but through different methods, such as venous blood, to see whether this yields similar results.

Based on these limitations, and on our analysis of previous studies, we conclude that reference studies that evaluate different ways of using objective health indicators like biomarkers in biosocial surveys are an important part of the research process: They can help establish the predictive value of those indicators for mortality, and create a basis for further research investigating the determinants and consequences of biomarkers gathered by population-based social surveys.

6. Conclusion

The results from our study show moderate gains in predictive power by adding four biomarkers into survival analytical models. Choosing the most parsimonious functional form, the risk index, comes at some cost of predictive power, but might be justified due to its simple nature and easy interpretation. The risk factor, risk group, and risk profile functional forms do not show strong differences, and a choice between them would

depend not on overall model quality but on whether certain specific risk group combinations need to be identified. For continuous biomarkers, especially CRP, whether individuals with acute illness are to be excluded from the analyses (which increases the predictive power) or whether they are to be included seems to play a role. While the total gain in predictive power might look sobering at first, we cannot expect to make phenomenal gains in predictive power using only four indicators which are, as all variables, subject to measurement error, and can only reflect the limited aspect of the organism's functioning that is relevant to morbidity and mortality. It has to be remembered that a major advantage of integrating biomarkers lies in their objective measurement, which makes them complementary to self-reported and subjective measures in large-scale population-based surveys.

The more different biomarkers are collected in standardized ways in biosocial surveys, the more important it becomes to assess how we can best operationalize these biomarkers for use in biodemographic research in the future. The present study can therefore only be a small step in a research process that needs updating with increasingly complex data as it becomes routinely available.

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Appendix

Table A-1: AUC for all models in the analyses

			Gross increase						Marginal increase		
			Baseline	Index	RF	Cont	RP	RG	Index	RF	RG
Mortality	Total sample	All	0.576	0.599	0.615	0.596	0.618	0.617	0.625	0.625	0.626
		CRP <= 10 mg/l	0.579	0.596	0.603	0.611	0.606	0.605	0.614	0.614	0.616
	Young men	All	0.534	0.587	0.612	0.596	0.615	0.622	0.629	0.635	0.641
All-cause		CRP <= 10 mg/l	0.541	0.584	0.594	0.607	0.599	0.602	0.618	0.626	0.634
	Young women	All	0.573	0.641	0.657	0.617	0.640	0.664	0.667	0.670	0.675
		CRP <= 10 mg/l	0.574	0.625	0.638	0.631	0.616	0.638	0.634	0.642	0.647
	Old men	All	0.522	0.552	0.601	0.548	0.604	0.595	0.614	0.616	0.620
		CRP <= 10 mg/l	0.534	0.563	0.592	0.589	0.591	0.590	0.602	0.604	0.607
	Old women	All	0.538	0.563	0.583	0.571	0.589	0.589	0.598	0.602	0.604
		CRP <= 10 mg/l	0.538	0.557	0.575	0.584	0.578	0.582	0.590	0.598	0.599
	Total sample	All	0.583	0.608	0.619	0.610	0.623	0.620	0.631	0.629	0.632
		CRP <= 10 mg/l	0.593	0.611	0.616	0.624	0.617	0.615	0.629	0.626	0.629
	Young men	All	0.590	0.669	0.694	0.668	0.694	0.689	0.716	0.718	0.720
		CRP <= 10 mg/l	0.591	0.662	0.681	0.674	0.695	0.679	0.716	0.713	0.721
CVD	Young women	All	0.606	0.677	0.676	0.646	0.658	0.680	0.684	0.681	0.690
		CRP <= 10 mg/l	0.647	0.698	0.688	0.678	0.681	0.710	0.703	0.702	0.726
	Old men	All	0.540	0.552	0.586	0.558	0.585	0.590	0.602	0.602	0.607
		CRP <= 10 mg/l	0.537	0.551	0.574	0.581	0.576	0.566	0.599	0.601	0.594
	Old women	All	0.544	0.576	0.595	0.585	0.604	0.592	0.610	0.613	0.611
		CRP <= 10 mg/l	0.546	0.576	0.589	0.593	0.589	0.585	0.605	0.610	0.609

Note: RF = risk factors; Cont = continuous biomarkers; RP = risk profiles; RG = risk groups.

Figure A-1: AUC over age for the total sample

a) all-cause mortality **b) CVD-mortality**

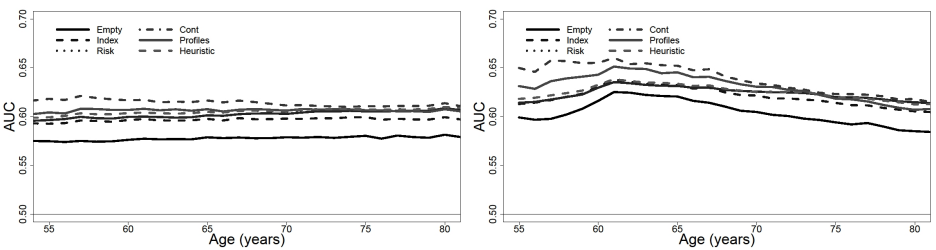

Table A-2.1: Hazard ratios from Cox-models on all-cause mortality with different functional forms on their own, total sample

	(1)		(2)		(3)		(4)		(5)	
Male	Ref.		Ref.		Ref.		Ref.		Ref.	
Female	0.66	[0.60,0.73]	0.64	[0.58,0.70]	0.67	[0.61,0.74]	0.64	[0.58,0.71]	0.63	[0.57,0.70]
White		Ref.		Ref.		Ref.		Ref.		Ref.
Black	1.24	[1.06,1.44]	1.18	[1.01,1.37]	1.21	[1.03,1.41]	1.22	[1.05,1.43]	1.18	[1.01,1.37]
Other	0.82	[0.62,1.10]	0.82	[0.61,1.10]	0.78	[0.58,1.05]	0.82	[0.61,1.10]	0.82	[0.61,1.09]
Age at measurement	1.00	[0.80,1.25]	0.99	[0.79,1.24]	1.01	[0.81,1.26]	1.01	[0.81,1.27]	0.99	[0.79,1.24]
Age^2	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
Number of risk factors										
0		Ref.								
1	1.43	[1.24,1.66]								
2	1.70	[1.45,1.98]								
3	2.20	[1.80,2.68]								
4	3.54	[2.41,5.21]								
Risk factors										
High ratio of TC to HDL (>5)			1.00	[0.88,1.14]						
High hbA1c (≥6.4%)			1.58	[1.40,1.78]						
High CRP (≥3.0 ug/mL)			1.77	[1.59,1.96]						
High risk systolic BP (>139)			1.00	[0.90,1.12]						
Continuous biomarkers										
Ratio of TC to HDL					1.04	[1.00,1.08]				
Blood glycated hemoglobin level					1.18	[1.13,1.23]				
Blood CRP level					1.01	[1.01,1.02]				
Systolic BP					1.00	[1.00,1.00]				
Risk profiles										
1								Ref.		
2							1.93	[1.55,2.39]		
3							1.31	[1.04,1.64]		
4							1.76	[1.43,2.18]		
5							1.64	[1.24,2.16]		
6							1.01	[0.80,1.27]		
7							3.10	[2.42,3.96]		
8							1.09	[0.87,1.38]		
9							0.86	[0.67,1.09]		
Risk groups										
0000										Ref.
0001									1.15	[0.95,1.40]
0010									1.95	[1.64,2.33]
0011									1.58	[1.27,1.96]
0100									1.48	[1.13,1.95]
0101									1.63	[1.21,2.20]
0110									3.18	[2.42,4.19]
0111									2.68	[2.03,3.55]
1000									1.03	[0.78,1.37]
1001									1.02	[0.72,1.45]
1010									1.82	[1.40,2.37]
1011									1.76	[1.33,2.35]
1100									1.36	[0.88,2.10]
1101									2.07	[1.26,3.37]
1110									2.69	[1.76,4.11]
1111									3.57	[2.43,5.26]
N	14,416		14,416		14,416		14,414		14,416	
AUC	0.599		0.615		0.596		0.618		0.617	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ included.

Table A-2.2: Hazard ratios from Cox-models on all-cause mortality with different functional forms on their own, total sample

	(1)		(2)		(3)		(4)		(5)	
Male	Ref.		Ref.		Ref.		Ref.		Ref.	
Female	0.65	[0.58,0.72]	0.64	[0.57,0.71]	0.63	[0.56,0.71]	0.64	[0.57,0.71]	0.63	[0.57,0.71]
White	Ref.		Ref.		Ref.		Ref.		Ref.	
Black	1.27	[1.07,1.51]	1.22	[1.03,1.45]	1.20	[1.00,1.42]	1.27	[1.07,1.51]	1.22	[1.02,1.45]
Other	0.87	[0.63,1.21]	0.86	[0.62,1.20]	0.85	[0.61,1.17]	0.86	[0.62,1.20]	0.86	[0.62,1.20]
Age at measurement	0.97	[0.75,1.25]	0.96	[0.74,1.23]	0.97	[0.75,1.25]	0.98	[0.76,1.27]	0.96	[0.74,1.23]
Age^2	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
Number of risk factors										
0		Ref.								
1	1.32	[1.14,1.53]								
2	1.45	[1.23,1.72]								
3	1.93	[1.55,2.40]								
4	2.84	[1.79,4.50]								
Risk factors										
High ratio of TC to HDL (>5)			0.96	[0.83,1.11]						
High hbA1c (≥6.4%)			1.56	[1.36,1.78]						
High CRP (≥3.0 ug/mL)			1.53	[1.36,1.73]						
High risk systolic BP (>139)			1.03	[0.91,1.16]						
Continuous biomarkers										
Ratio of TC to HDL					1.00	[0.95,1.05]				
Blood glycated hemoglobin level					1.18	[1.13,1.24]				
Blood CRP level					1.11	[1.08,1.14]				
Systolic BP					1.00	[1.00,1.00]				
Risk profiles										
1							Ref.			
2							1.70	[1.34,2.15]		
3							1.28	[1.00,1.64]		
4							1.49	[1.18,1.88]		
5							1.42	[1.05,1.93]		
6							1.02	[0.81,1.30]		
7							2.93	[2.21,3.89]		
8							1.09	[0.85,1.38]		
9							0.87	[0.68,1.11]		
Risk groups										
0000									Ref.	
0001									1.15	[0.95,1.40]
0010									1.72	[1.42,2.08]
0011									1.31	[1.02,1.69]
0100									1.43	[1.07,1.90]
0101									1.61	[1.19,2.19]
0110									2.78	[1.99,3.89]
0111									2.64	[1.91,3.64]
1000									1.04	[0.78,1.38]
1001									0.97	[0.69,1.37]
1010									1.52	[1.09,2.10]
1011									1.49	[1.07,2.07]
1100									1.32	[0.84,2.06]
1101									2.06	[1.26,3.39]
1110									2.04	[1.16,3.58]
1111									2.86	[1.80,4.54]
N	12607		12607		12607		12605		12607	
AUC	0.596		0.603		0.611		0.606		0.605	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-2.3: Hazard ratios from Cox-models on all-cause mortality with different functional forms on their own, men 50–69

	(1)		(2)		(3)		(4)		(5)	
Male	Ref.		Ref.		Ref.		Ref.		Ref.	
Female										
White	Ref.		Ref.		Ref.		Ref.		Ref.	
Black	1.41	[0.96,2.05]	1.32	[0.91,1.94]	1.49	[1.03,2.15]	1.47	[1.01,2.13]	1.31	[0.89,1.94]
Other	0.87	[0.47,1.58]	0.89	[0.49,1.61]	0.92	[0.50,1.69]	0.91	[0.49,1.67]	0.88	[0.49,1.60]
Age at measurement	0.50	[0.16,1.58]	0.50	[0.16,1.59]	0.50	[0.16,1.62]	0.53	[0.17,1.66]	0.52	[0.16,1.65]
Age^2	1.01	[1.00,1.02]	1.01	[1.00,1.02]	1.01	[1.00,1.02]	1.01	[1.00,1.01]	1.01	[1.00,1.01]
Number of risk factors										
0	Ref.									
1	1.96	[1.32,2.91]								
2	2.34	[1.53,3.58]								
3	2.82	[1.69,4.71]								
4	3.26	[0.85,12.53]								
Risk factors										
High ratio of TC to HDL (>5)			0.91	[0.66,1.25]						
High hbA1c (≥6.4%)			1.56	[1.14,2.14]						
High CRP (≥3.0 ug/mL)			2.13	[1.60,2.83]						
High risk systolic BP (>139)			1.12	[0.84,1.51]						
Continuous biomarkers										
Ratio of TC to HDL					1.06	[0.97,1.16]				
Blood glycated hemoglobin level					1.10	[1.00,1.20]				
Blood CRP level					1.04	[1.03,1.05]				
Systolic BP					1.00	[1.00,1.01]				
Risk profiles										
1							Ref.			
2							3.19	[1.63,6.22]		
3							2.35	[1.12,4.93]		
4							2.94	[1.48,5.81]		
5							2.33	[1.14,4.76]		
6							1.66	[0.83,3.32]		
7							3.22	[1.58,6.56]		
8							1.10	[0.50,2.42]		
9							0.99	[0.46,2.14]		
Risk groups										
0000									Ref.	
0001									1.78	[1.09,2.93]
0010									2.92	[1.80,4.72]
0011									2.51	[1.43,4.40]
0100									1.94	[0.94,3.98]
0101									2.33	[0.97,5.58]
0110									5.10	[2.55,10.21]
0111									2.84	[1.20,6.70]
1000									1.18	[0.60,2.32]
1001									0.85	[0.29,2.52]
1010									2.71	[1.42,5.17]
1011									2.23	[1.02,4.88]
1100									1.17	[0.38,3.62]
1101									3.96	[1.69,9.26]
1110									3.13	[1.03,9.48]
1111									3.27	[0.85,12.54]
N	3627		3627		3627		3626		3627	
AUC	0.587		0.612		0.596		0.615		0.622	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ included.

Table A-2.4: Hazard ratios from Cox-models on all-cause mortality with different functional forms on their own, men 50–69

	(1)		(2)		(3)		(4)		(5)	
Male	Ref.		Ref.		Ref.		Ref.		Ref.	
Female										
White	Ref.		Ref.		Ref.		Ref.		Ref.	
Black	1.26	[0.82,1.95]	1.20	[0.77,1.86]	1.22	[0.79,1.88]	1.36	[0.88,2.08]	1.17	[0.75,1.84]
Other	1.01	[0.54,1.90]	1.01	[0.55,1.88]	1.03	[0.54,1.94]	1.03	[0.54,1.96]	1.01	[0.54,1.87]
Age at measurement	0.57	[0.16,1.99]	0.57	[0.16,1.99]	0.54	[0.15,1.92]	0.60	[0.17,2.09]	0.57	[0.16,2.03]
Age^2	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.01	[0.99,1.02]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Number of risk factors										
0	Ref.									
1	1.93	[1.27,2.95]								
2	1.75	[1.08,2.83]								
3	2.92	[1.66,5.14]								
4	2.90	[0.66,12.78]								
Risk factors										
High ratio of TC to HDL (>5)			0.89	[0.61,1.29]						
High hbA1c (≥6.4%)			1.51	[1.06,2.16]						
High CRP (≥3.0 ug/mL)			1.75	[1.26,2.43]						
High risk systolic BP (>139)			1.31	[0.95,1.81]						
Continuous biomarkers										
Ratio of TC to HDL					1.03	[0.93,1.15]				
Blood glycated hemoglobin level					1.06	[0.96,1.18]				
Blood CRP level					1.18	[1.11,1.25]				
Systolic BP					1.01	[1.00,1.02]				
Risk profiles										
1							Ref.			
2							3.01	[1.47,6.15]		
3							2.42	[1.15,5.07]		
4							2.17	[1.00,4.69]		
5							1.96	[0.90,4.24]		
6							1.63	[0.82,3.25]		
7							2.32	[1.04,5.18]		
8							1.06	[0.48,2.32]		
9							0.99	[0.45,2.16]		
Risk groups										
0000									Ref.	
0001									1.97	[1.19,3.27]
0010									2.69	[1.56,4.64]
0011									1.93	[0.97,3.85]
0100									2.00	[0.98,4.09]
0101									2.45	[0.99,6.04]
0110									3.75	[1.47,9.57]
0111									2.62	[0.99,6.95]
1000									1.20	[0.58,2.50]
1001									0.79	[0.26,2.40]
1010									1.83	[0.78,4.26]
1011									2.81	[1.22,6.47]
1100									1.06	[0.34,3.27]
1101									4.10	[1.78,9.47]
1110									1.88	[0.27,13.03]
1111									2.93	[0.66,12.95]
N	3627		3627		3627		3626		3627	
AUC	0.584		0.594		0.607		0.599		0.602	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-2.5: Hazard ratios from Cox-models on all-cause mortality with different functional forms on their own, women 50–69

	(1)		(2)		(3)		(4)		(5)	
Male										
Female		Ref.		Ref.		Ref.		Ref.		Ref.
White		Ref.		Ref.		Ref.		Ref.		Ref.
Black	1.36	[0.96,1.93]	1.28	[0.90,1.82]	1.31	[0.91,1.88]	1.39	[0.97,1.99]	1.27	[0.89,1.81]
Other	0.70	[0.37,1.30]	0.68	[0.36,1.29]	0.70	[0.37,1.32]	0.71	[0.37,1.34]	0.69	[0.36,1.31]
Age at measurement	0.79	[0.25,2.56]	0.82	[0.25,2.66]	0.87	[0.27,2.86]	0.77	[0.24,2.49]	0.84	[0.26,2.71]
Age^2	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Number of risk factors										
0		Ref.								
1	1.77	[1.12,2.80]								
2	2.97	[1.86,4.75]								
3	3.42	[1.85,6.34]								
4	7.10	[3.26,15.50]								
Risk factors										
High ratio of TC to HDL (>5)			1.06	[0.73,1.53]						
High hbA1c (≥6.4%)			2.33	[1.67,3.26]						
High CRP (≥3.0 ug/mL)			2.18	[1.59,2.98]						
High risk systolic BP (>139)			1.11	[0.79,1.56]						
Continuous biomarkers										
Ratio of TC to HDL					1.10	[0.96,1.25]				
Blood glycated hemoglobin level					1.29	[1.16,1.43]				
Blood CRP level					1.02	[1.02,1.03]				
Systolic BP					1.00	[0.99,1.01]				
Risk profiles										
1								Ref.		
2							1.46	[0.74,2.89]		
3							1.55	[0.67,3.59]		
4							1.59	[0.89,2.82]		
5							1.73	[0.76,3.94]		
6							0.56	[0.25,1.25]		
7							4.43	[2.36,8.30]		
8							0.88	[0.42,1.83]		
9							0.57	[0.25,1.29]		
Risk groups										
0000										Ref.
0001									1.44	[0.68,3.06]
0010									2.14	[1.31,3.49]
0011									2.25	[1.14,4.44]
0100									2.03	[0.68,6.06]
0101									4.15	[1.78,9.67]
0110									5.79	[3.08,10.90]
0111									4.48	[1.94,10.34]
1000									1.03	[0.44,2.42]
1001									1.08	[0.13,9.26]
1010									2.76	[1.49,5.12]
1011									1.92	[0.66,5.56]
1100									0.33	[0.04,2.52]
1101									1.39	[0.26,7.40]
1110									5.80	[2.44,13.80]
1111									7.15	[3.28,15.59]
N	4945		4945		4945		4945		4945	
AUC	0.641		0.657		0.617		0.640		0.664	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ included.

Table A-2.6: Hazard ratios from Cox-models on all-cause mortality with different functional forms on their own, women 50–69

	(1)		(2)		(3)		(4)		(5)	
Male										
Female		Ref.		Ref.		Ref.		Ref.		Ref.
White		Ref.		Ref.		Ref.		Ref.		Ref.
Black	1.55	[1.02,2.36]	1.43	[0.93,2.19]	1.42	[0.92,2.20]	1.49	[0.97,2.31]	1.41	[0.91,2.17]
Other	0.82	[0.39,1.72]	0.80	[0.38,1.70]	0.81	[0.39,1.71]	0.80	[0.37,1.70]	0.81	[0.37,1.73]
Age at measurement	0.87	[0.21,3.59]	0.84	[0.20,3.48]	0.81	[0.19,3.35]	0.84	[0.20,3.45]	0.86	[0.20,3.58]
Age^2	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Number of risk factors										
0		Ref.								
1	1.47	[0.90,2.38]								
2	2.17	[1.29,3.64]								
3	2.71	[1.32,5.57]								
4	3.71	[1.16,11.86]								
Risk factors										
High ratio of TC to HDL (>5)			0.85	[0.51,1.39]						
High hbA1c (≥6.4%)			2.44	[1.61,3.69]						
High CRP (≥3.0 ug/mL)			1.66	[1.16,2.37]						
High risk systolic BP (>139)			1.21	[0.81,1.81]						
Continuous biomarkers										
Ratio of TC to HDL					0.98	[0.83,1.17]				
Blood glycated hemoglobin level					1.31	[1.16,1.47]				
Blood CRP level					1.11	[1.04,1.19]				
Systolic BP					1.00	[0.99,1.01]				
Risk profiles										
1								Ref.		
2							1.03	[0.47,2.27]		
3							1.46	[0.59,3.61]		
4							1.05	[0.55,1.99]		
5							0.92	[0.31,2.70]		
6							0.59	[0.27,1.29]		
7							4.01	[1.99,8.09]		
8							0.85	[0.40,1.77]		
9							0.55	[0.24,1.29]		
Risk groups										
0000										Ref.
0001									1.41	[0.68,2.94]
0010									1.62	[0.93,2.84]
0011									1.66	[0.71,3.90]
0100									2.00	[0.66,6.04]
0101									4.04	[1.77,9.22]
0110									5.09	[2.49,10.42]
0111									4.80	[1.86,12.39]
1000									1.04	[0.44,2.46]
1001									1.00	[0.11,9.06]
1010									1.55	[0.66,3.65]
1011									1.57	[0.47,5.18]
1100									0.31	[0.04,2.24]
1101									1.27	[0.27,6.06]
1110									3.84	[0.90,16.43]
1111									3.77	[1.18,12.05]
N	4264		4264		4264		4264		4264	
AUC	0.625		0.638		0.631		0.616		0.638	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-2.7: Hazard ratios from Cox-models on all-cause mortality with different functional forms on their own, men 70–89

	(1)		(2)		(3)		(4)		(5)	
Male		Ref.		Ref.		Ref.		Ref.		Ref.
Female										
White		Ref.		Ref.		Ref.		Ref.		Ref.
Black	1.13	[0.88,1.45]	1.07	[0.83,1.37]	1.11	[0.86,1.43]	1.10	[0.85,1.42]	1.07	[0.83,1.38]
Other	0.84	[0.49,1.43]	0.83	[0.49,1.41]	0.78	[0.46,1.34]	0.84	[0.49,1.43]	0.83	[0.49,1.40]
Age at measurement	0.96	[0.47,1.96]	0.91	[0.44,1.86]	1.02	[0.50,2.10]	0.94	[0.46,1.93]	0.90	[0.44,1.85]
Age^2	1.00	[1.00,1.00]	1.00	[1.00,1.01]	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.01]
Number of risk factors										
0		Ref.								
1	1.28	[1.03,1.60]								
2	1.36	[1.08,1.71]								
3	1.82	[1.36,2.44]								
4	1.91	[0.90,4.04]								
Risk factors										
High ratio of TC to HDL (>5)			0.87	[0.70,1.07]						
High hbA1c (≥6.4%)			1.26	[1.05,1.52]						
High CRP (≥3.0 ug/mL)			1.83	[1.56,2.15]						
High risk systolic BP (>139)			0.91	[0.78,1.07]						
Continuous biomarkers										
Ratio of TC to HDL					0.97	[0.90,1.04]				
Blood glycated hemoglobin level					1.13	[1.05,1.22]				
Blood CRP level					1.01	[1.00,1.01]				
Systolic BP					1.00	[0.99,1.00]				
Risk profiles										
1								Ref.		
2							1.96	[1.44,2.67]		
3							1.04	[0.73,1.50]		
4							1.60	[1.15,2.23]		
5							1.40	[0.92,2.15]		
6							0.85	[0.60,1.21]		
7							2.44	[1.62,3.65]		
8							1.21	[0.85,1.71]		
9							0.87	[0.60,1.26]		
Risk groups										
0000										Ref.
0001									0.97	[0.74,1.28]
0010									1.97	[1.51,2.57]
0011									1.46	[1.08,1.99]
0100									1.20	[0.79,1.83]
0101									1.12	[0.73,1.72]
0110									2.37	[1.57,3.57]
0111									2.70	[1.84,3.97]
1000									0.98	[0.64,1.51]
1001									0.88	[0.54,1.43]
1010									1.45	[0.94,2.22]
1011									1.60	[1.05,2.45]
1100									1.10	[0.54,2.26]
1101									0.51	[0.13,2.04]
1110									1.86	[0.89,3.89]
1111									1.91	[0.90,4.05]
N	2506		2506		2506		2505		2506	
AUC	0.552		0.601		0.548		0.604		0.595	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ included.

Table A-2.8: Hazard ratios from Cox-models on all-cause mortality with different functional forms on their own, men 70–89

	(1)		(2)		(3)		(4)		(5)	
Male		Ref.		Ref.		Ref.		Ref.		Ref.
Female										
White		Ref.		Ref.		Ref.		Ref.		Ref.
Black	1.24	[0.95,1.61]	1.19	[0.91,1.54]	1.16	[0.89,1.52]	1.23	[0.95,1.61]	1.18	[0.91,1.55]
Other	0.72	[0.40,1.32]	0.72	[0.39,1.31]	0.73	[0.40,1.32]	0.72	[0.40,1.32]	0.73	[0.40,1.32]
Age at measurement	0.82	[0.37,1.82]	0.76	[0.35,1.69]	0.82	[0.37,1.81]	0.80	[0.36,1.75]	0.76	[0.34,1.70]
Age^2	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]
Number of risk factors										
0		Ref.								
1	1.18	[0.94,1.48]								
2	1.32	[1.03,1.69]								
3	1.49	[1.06,2.09]								
4	1.84	[0.70,4.84]								
Risk factors										
High ratio of TC to HDL (>5)			0.85	[0.68,1.07]						
High hbA1c (≥6.4%)			1.26	[1.02,1.56]						
High CRP (≥3.0 ug/mL)			1.70	[1.42,2.03]						
High risk systolic BP (>139)			0.91	[0.77,1.09]						
Continuous biomarkers										
Ratio of TC to HDL					0.94	[0.87,1.01]				
Blood glycated hemoglobin level					1.13	[1.04,1.24]				
Blood CRP level					1.11	[1.07,1.15]				
Systolic BP					1.00	[0.99,1.00]				
Risk profiles										
1								Ref.		
2							1.74	[1.23,2.47]		
3							1.02	[0.70,1.49]		
4							1.50	[1.04,2.17]		
5							1.37	[0.89,2.13]		
6							0.88	[0.62,1.25]		
7							2.57	[1.62,4.07]		
8							1.18	[0.82,1.71]		
9							0.90	[0.62,1.32]		
Risk groups										
0000										Ref.
0001									0.98	[0.75,1.29]
0010									1.76	[1.31,2.36]
0011									1.40	[0.98,2.00]
0100									1.17	[0.75,1.83]
0101									1.15	[0.74,1.78]
0110									2.61	[1.62,4.21]
0111									2.50	[1.57,4.00]
1000									0.98	[0.61,1.56]
1001									0.83	[0.49,1.41]
1010									1.53	[0.93,2.52]
1011									1.29	[0.79,2.11]
1100									1.17	[0.58,2.39]
1101									0.52	[0.14,1.99]
1110									1.40	[0.60,3.25]
1111									1.84	[0.70,4.86]
N	2165		2165		2165		2164		2165	
AUC	0.552		0.601		0.548		0.604		0.595	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-2.9: Hazard ratios from Cox-models on all-cause mortality with different functional forms on their own, women 70–89

	(1)		(2)		(3)		(4)		(5)	
Male										
Female		Ref.		Ref.		Ref.		Ref.		Ref.
White		Ref.		Ref.		Ref.		Ref.		Ref.
Black	1.05	[0.82,1.33]	1.01	[0.79,1.29]	1.00	[0.78,1.29]	1.02	[0.80,1.31]	1.00	[0.78,1.28]
Other	0.85	[0.51,1.41]	0.85	[0.51,1.41]	0.80	[0.48,1.33]	0.80	[0.48,1.35]	0.78	[0.47,1.31]
Age at measurement	1.30	[0.67,2.53]	1.28	[0.66,2.49]	1.30	[0.67,2.53]	1.33	[0.68,2.61]	1.30	[0.67,2.52]
Age^2	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]
Number of risk factors										
0		Ref.								
1	1.17	[0.94,1.46]								
2	1.29	[1.01,1.65]								
3	1.79	[1.33,2.41]								
4	3.95	[2.38,6.56]								
Risk factors										
High ratio of TC to HDL (>5)			1.16	[0.95,1.43]						
High hbA1c (≥6.4%)			1.61	[1.33,1.95]						
High CRP (≥3.0 ug/mL)			1.37	[1.17,1.62]						
High risk systolic BP (>139)			0.96	[0.81,1.13]						
Continuous biomarkers										
Ratio of TC to HDL					1.06	[0.99,1.14]				
Blood glycated hemoglobin level					1.23	[1.14,1.33]				
Blood CRP level					1.01	[1.00,1.02]				
Systolic BP					1.00	[1.00,1.00]				
Risk profiles										
1								Ref.		
2							1.70	[1.20,2.39]		
3							1.22	[0.88,1.69]		
4							1.64	[1.19,2.26]		
5							1.60	[0.98,2.63]		
6							1.06	[0.73,1.56]		
7							3.22	[2.20,4.71]		
8							1.16	[0.81,1.67]		
9							0.92	[0.65,1.30]		
Risk groups										
0000										Ref.
0001									1.30	[0.95,1.77]
0010									1.49	[1.06,2.10]
0011									1.33	[0.89,2.00]
0100									1.83	[1.16,2.88]
0101									1.61	[1.00,2.61]
0110									3.83	[2.26,6.47]
0111									3.56	[2.16,5.87]
1000									1.08	[0.67,1.74]
1001									1.17	[0.70,1.94]
1010									1.09	[0.61,1.93]
1011									1.29	[0.73,2.29]
1100									1.22	[0.55,2.67]
1101									2.89	[1.46,5.74]
1110									3.29	[1.45,7.46]
1111									3.95	[1.91,8.15]
N	3338		3338		3338		3338		3338	
AUC	0.563		0.583		0.571		0.589		0.589	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ included.

Table A-2.10: Hazard ratios from Cox-models on all-cause mortality with different functional forms on their own, women 70–89

	(1)		(2)		(3)		(4)		(5)	
Male										
Female		Ref.		Ref.		Ref.		Ref.		Ref.
White		Ref.		Ref.		Ref.		Ref.		Ref.
Black	1.06	[0.80,1.41]	1.02	[0.77,1.36]	1.01	[0.76,1.34]	1.06	[0.80,1.41]	1.03	[0.77,1.37]
Other	0.84	[0.48,1.47]	0.83	[0.47,1.48]	0.74	[0.42,1.30]	0.79	[0.45,1.41]	0.76	[0.42,1.35]
Age at measurement	1.38	[0.66,2.88]	1.34	[0.64,2.79]	1.38	[0.66,2.87]	1.45	[0.69,3.05]	1.39	[0.66,2.89]
Age^2	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]
Number of risk factors										
0		Ref.								
1	1.08	[0.86,1.37]								
2	1.18	[0.91,1.53]								
3	1.61	[1.14,2.28]								
4	3.35	[1.79,6.28]								
Risk factors										
High ratio of TC to HDL (>5)			1.18	[0.94,1.47]						
High hbA1c (≥6.4%)			1.61	[1.30,1.99]						
High CRP (≥3.0 ug/mL)			1.24	[1.03,1.49]						
High risk systolic BP (>139)			0.92	[0.76,1.10]						
Continuous biomarkers										
Ratio of TC to HDL					1.05	[0.97,1.13]				
Blood glycated hemoglobin level					1.29	[1.20,1.38]				
Blood CRP level					1.07	[1.03,1.11]				
Systolic BP					1.00	[0.99,1.00]				
Risk profiles										
1								Ref.		
2							1.46	[0.98,2.17]		
3							1.20	[0.83,1.74]		
4							1.56	[1.09,2.23]		
5							1.45	[0.82,2.56]		
6							1.09	[0.74,1.60]		
7							3.37	[2.17,5.23]		
8							1.16	[0.81,1.68]		
9							0.93	[0.64,1.35]		
Risk groups										
0000										Ref.
0001									0.89	[0.66,1.20]
0010									1.39	[1.03,1.87]
0011									0.88	[0.57,1.35]
0100									1.24	[0.81,1.89]
0101									1.49	[0.88,2.50]
0110									1.40	[0.78,2.49]
0111									2.06	[1.19,3.56]
1000									1.02	[0.65,1.60]
1001									1.04	[0.64,1.71]
1010									1.36	[0.80,2.32]
1011									1.08	[0.63,1.84]
1100									1.96	[0.96,3.99]
1101									2.69	[1.38,5.24]
1110									1.97	[0.88,4.38]
1111									3.41	[1.81,6.43]
N	2911		2911		2911		2911		2911	
AUC	0.557		0.575		0.584		0.578		0.582	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-2.11: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms on their own, total sample

	(1)		(2)		(3)		(4)		(5)	
Male		Ref.		Ref.		Ref.		Ref.		Ref.
Female	0.70	[0.59,0.82]	0.69	[0.58,0.81]	0.72	[0.61,0.85]	0.69	[0.59,0.82]	0.68	[0.58,0.80]
White		Ref.		Ref.		Ref.		Ref.		Ref.
Black	1.34	[1.06,1.69]	1.26	[0.99,1.59]	1.26	[0.99,1.60]	1.31	[1.03,1.66]	1.25	[0.99,1.59]
Other	0.87	[0.54,1.39]	0.85	[0.53,1.36]	0.79	[0.49,1.26]	0.84	[0.52,1.35]	0.85	[0.53,1.36]
Age at measurement	1.25	[0.87,1.81]	1.23	[0.85,1.77]	1.26	[0.87,1.82]	1.27	[0.88,1.84]	1.22	[0.85,1.76]
Age^2	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
Number of risk factors										
0		Ref.								
1	1.53	[1.21,1.95]								
2	1.86	[1.44,2.39]								
3	2.71	[1.97,3.71]								
4	4.19	[2.18,8.03]								
Risk factors										
High ratio of TC to HDL (>5)			0.99	[0.81,1.22]						
High hbA1c (≥6.4%)			1.86	[1.54,2.26]						
High CRP (≥3.0 ug/mL)			1.72	[1.45,2.03]						
High risk systolic BP (>139)			1.12	[0.94,1.33]						
Continuous biomarkers										
Ratio of TC to HDL					1.05	[0.98,1.12]				
Blood glycated hemoglobin level					1.28	[1.21,1.36]				
Blood CRP level					1.01	[1.01,1.02]				
Systolic BP					1.00	[1.00,1.01]				
Risk profiles										
1								Ref.		
2							1.91	[1.37,2.66]		
3							1.35	[0.95,1.90]		
4							1.50	[1.06,2.10]		
5							1.91	[1.23,2.94]		
6							1.01	[0.71,1.43]		
7							3.97	[2.70,5.83]		
8							1.05	[0.71,1.55]		
9							0.86	[0.59,1.25]		
Risk groups										
0000										Ref.
0001									1.33	[0.99,1.80]
0010									1.86	[1.40,2.49]
0011									1.83	[1.30,2.58]
0100									1.97	[1.29,3.03]
0101									1.62	[1.00,2.61]
0110									4.18	[2.68,6.50]
0111									3.38	[2.16,5.30]
1000									1.11	[0.70,1.75]
1001									1.23	[0.75,2.03]
1010									1.58	[1.01,2.46]
1011									1.98	[1.27,3.09]
1100									1.28	[0.60,2.74]
1101									2.84	[1.46,5.54]
1110									3.56	[1.81,7.02]
1111									4.24	[2.21,8.14]
N	14416		14416		14416		14414		14416	
AUC	0.608		0.619		0.610		0.623		0.620	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ included.

Table A-2.12: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms on their own, total sample

	(1)		(2)		(3)		(4)		(5)	
Male	Ref.		Ref.		Ref.		Ref.		Ref.	
Female	0.68	[0.57,0.82]	0.68	[0.57,0.82]	0.69	[0.57,0.83]	0.69	[0.58,0.83]	0.68	[0.57,0.82]
White	Ref.		Ref.		Ref.		Ref.		Ref.	
Black	1.27	[0.98,1.65]	1.21	[0.93,1.57]	1.18	[0.91,1.53]	1.25	[0.96,1.62]	1.19	[0.91,1.55]
Other	0.81	[0.47,1.42]	0.79	[0.45,1.38]	0.74	[0.42,1.29]	0.76	[0.43,1.35]	0.79	[0.45,1.38]
Age at measurement	1.45	[0.94,2.23]	1.42	[0.92,2.18]	1.43	[0.92,2.22]	1.48	[0.96,2.29]	1.41	[0.91,2.16]
Age^2	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
Number of risk factors										
0	Ref.									
1	0.95	[0.75,1.20]								
2	1.99	[1.61,2.47]								
3	1.41	[1.17,1.71]								
4	1.13	[0.93,1.37]								
Risk factors										
High ratio of TC to HDL (>5)			0.95	[0.75,1.20]						
High hbA1c (≥6.4%)			1.99	[1.61,2.47]						
High CRP (≥3.0 ug/mL)			1.41	[1.17,1.71]						
High risk systolic BP (>139)			1.13	[0.93,1.37]						
Continuous biomarkers										
Ratio of TC to HDL					1.01	[0.93,1.09]				
Blood glycated hemoglobin level					1.32	[1.24,1.40]				
Blood CRP level					1.08	[1.04,1.12]				
Systolic BP					1.00	[1.00,1.01]				
Risk profiles										
1							Ref.			
2							1.47	[0.99,2.18]		
3							1.37	[0.95,1.98]		
4							1.12	[0.75,1.67]		
5							1.56	[0.98,2.50]		
6							1.02	[0.71,1.46]		
7							4.37	[2.85,6.70]		
8							1.09	[0.73,1.61]		
9							0.90	[0.61,1.32]		
Risk groups										
0000									Ref.	
0001									1.30	[0.95,1.77]
0010									1.49	[1.06,2.10]
0011									1.33	[0.89,2.00]
0100									1.83	[1.16,2.88]
0101									1.61	[1.00,2.61]
0110									3.83	[2.26,6.47]
0111									3.56	[2.16,5.87]
1000									1.08	[0.67,1.74]
1001									1.17	[0.70,1.94]
1010									1.09	[0.61,1.93]
1011									1.29	[0.73,2.29]
1100									1.22	[0.55,2.67]
1101									2.89	[1.46,5.74]
1110									3.29	[1.45,7.46]
1111									3.95	[1.91,8.15]
N	12607		12607		12607		12605		12607	
AUC	0.611		0.616		0.624		0.617		0.615	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-2.13: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms on their own, men 50–69

	(1)	(2)	(3)	(4)	(5)
Male	Ref.	Ref.	Ref.	Ref.	Ref.
Female					
White	Ref.	Ref.	Ref.	Ref.	Ref.
Black	1.29 [0.66,2.51]	1.07 [0.54,2.14]	1.43 [0.74,2.74]	1.34 [0.69,2.61]	1.09 [0.54,2.21]
Other	0.81 [0.31,2.16]	0.78 [0.29,2.09]	0.84 [0.31,2.32]	0.88 [0.32,2.39]	0.79 [0.29,2.13]
Age at measurement	1.74 [0.18,16.93]	1.75 [0.17,18.12]	2.11 [0.20,22.45]	2.01 [0.20,20.08]	1.90 [0.18,20.36]
Age^2	1.00 [0.98,1.01]	1.00 [0.98,1.02]	0.99 [0.98,1.01]	1.00 [0.98,1.01]	1.00 [0.98,1.01]
Number of risk factors					
0	Ref.				
1	3.81 [1.71,8.49]				
2	6.30 [2.83,14.02]				
3	9.35 [3.70,23.62]				
4	17.68 [3.90,80.21]				
Risk factors					
High ratio of TC to HDL (>5)		0.83 [0.45,1.54]			
High hbA1c (≥6.4%)		2.92 [1.70,4.99]			
High CRP (≥3.0 ug/mL)		3.29 [1.99,5.43]			
High risk systolic BP (>139)		1.48 [0.87,2.50]			
Continuous biomarkers					
Ratio of TC to HDL			1.14 [0.99,1.32]		
Blood glycated hemoglobin level			1.29 [1.16,1.44]		
Blood CRP level			1.04 [1.03,1.06]		
Systolic BP			1.01 [1.00,1.02]		
Risk profiles					
1				Ref.	
2				4.91 [1.44,16.71]	
3				2.27 [0.55,9.37]	
4				2.35 [0.58,9.52]	
5				3.88 [1.05,14.36]	
6				0.86 [0.23,3.23]	
7				7.51 [2.14,26.39]	
8				1.62 [0.40,6.51]	
9				1.32 [0.32,5.38]	
Risk groups					
0000					Ref.
0001					3.61 [1.38,9.46]
0010					5.68 [2.13,15.12]
0011					7.95 [2.99,21.15]
0100					5.34 [1.49,19.15]
0101					4.59 [1.03,20.51]
0110					21.42 [7.14,64.29]
0111					13.12 [4.01,42.96]
1000					1.59 [0.35,7.17]
1001					1.72 [0.30,10.05]
1010					4.02 [1.03,15.72]
1011					4.63 [0.87,24.58]
1100					0.00 [0.00,2.66e+09]
1101					11.20 [2.83,44.28]
1110					13.62 [2.56,72.55]
1111					17.79 [3.93,80.59]
N	3627	3627	3627	3626	3627
AUC	0.669	0.694	0.668	0.694	0.689

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ included.

Table A-2.14: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms on their own, men 50–69

	(1)	(2)	(3)	(4)	(5)
Male	Ref.	Ref.	Ref.	Ref.	Ref.
Female					
White	Ref.	Ref.	Ref.	Ref.	Ref.
Black	0.91 [0.46,1.79]	0.79 [0.40,1.57]	0.90 [0.46,1.76]	1.00 [0.51,1.98]	0.78 [0.38,1.58]
Other	0.83 [0.28,2.47]	0.78 [0.26,2.34]	0.82 [0.26,2.55]	0.86 [0.28,2.69]	0.79 [0.26,2.42]
Age at measurement	1.10 [0.08,14.81]	1.08 [0.08,15.16]	1.10 [0.07,16.08]	1.20 [0.09,16.54]	1.16 [0.08,16.86]
Age^2	1.00 [0.98,1.02]	1.00 [0.98,1.02]	1.00 [0.98,1.02]	1.00 [0.98,1.02]	1.00 [0.98,1.02]
Number of risk factors					
0	Ref.				
1	3.67 [1.61,8.33]				
2	3.74 [1.52,9.19]				
3	10.22 [3.99,26.16]				
4	18.85 [3.83,92.77]				
Risk factors					
High ratio of TC to HDL (>5)		1.00 [0.53,1.88]			
High hbA1c (≥6.4%)		3.01 [1.69,5.37]			
High CRP (≥3.0 ug/mL)		2.56 [1.45,4.52]			
High risk systolic BP (>139)		1.63 [0.91,2.94]			
Continuous biomarkers					
Ratio of TC to HDL			1.11 [0.95,1.30]		
Blood glycated hemoglobin level			1.25 [1.11,1.41]		
Blood CRP level			1.22 [1.10,1.36]		
Systolic BP			1.01 [1.00,1.03]		
Risk profiles					
1				Ref.	
2				3.94 [1.07,14.58]	
3				2.44 [0.61,9.76]	
4				0.60 [0.07,4.79]	
5				3.55 [0.94,13.39]	
6				0.82 [0.21,3.15]	
7				6.01 [1.62,22.28]	
8				1.60 [0.40,6.40]	
9				1.35 [0.33,5.43]	
Risk groups					
0000					Ref.
0001					3.69 [1.40,9.74]
0010					5.32 [1.85,15.26]
0011					3.41 [0.88,13.14]
0100					5.37 [1.53,18.88]
0101					4.39 [0.86,22.42]
0110					13.58 [2.99,61.62]
0111					14.48 [4.33,48.48]
1000					1.59 [0.33,7.66]
1001					1.94 [0.35,10.81]
1010					3.38 [0.73,15.60]
1011					5.78 [1.04,32.22]
1100					0.04 [0.00,53779198.32]
1101					12.19 [3.21,46.27]
1110					12.36 [1.65,92.53]
1111					19.15 [3.88,94.60]
N	3627	3627	3627	3626	3627
AUC	0.662	0.681	0.674	0.695	0.679

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-2.15: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms on their own, women 50–69

	(1)		(2)		(3)		(4)		(5)	
Male										
Female		Ref.		Ref.		Ref.		Ref.		Ref.
White		Ref.		Ref.		Ref.		Ref.		Ref.
Black	1.41	[0.80,2.50]	1.30	[0.73,2.33]	1.20	[0.65,2.21]	1.38	[0.75,2.53]	1.29	[0.72,2.31]
Other	1.16	[0.44,3.09]	1.10	[0.41,2.94]	1.09	[0.40,2.92]	1.08	[0.40,2.96]	1.10	[0.40,3.01]
Age at measurement	0.33	[0.04,3.01]	0.35	[0.04,3.21]	0.33	[0.04,3.14]	0.32	[0.04,2.88]	0.35	[0.04,3.24]
Age^2	1.01	[0.99,1.03]	1.01	[0.99,1.03]	1.01	[0.99,1.03]	1.01	[0.99,1.03]	1.01	[0.99,1.03]
Number of risk factors										
0		Ref.								
1	2.12	[0.82,5.48]								
2	3.92	[1.55,9.89]								
3	4.65	[1.55,13.98]								
4	7.45	[1.68,32.94]								
Risk factors										
High ratio of TC to HDL (>5)			1.10	[0.60,2.01]						
High hbA1c (≥6.4%)			3.10	[1.68,5.72]						
High CRP (≥3.0 ug/mL)			1.97	[1.11,3.47]						
High risk systolic BP (>139)			1.17	[0.63,2.16]						
Continuous biomarkers										
Ratio of TC to HDL					1.10	[0.91,1.32]				
Blood glycated hemoglobin level					1.46	[1.26,1.70]				
Blood CRP level					1.02	[1.02,1.03]				
Systolic BP					1.00	[0.98,1.02]				
Risk profiles										
1								Ref.		
2							1.52	[0.47,4.97]		
3							1.76	[0.49,6.35]		
4							1.68	[0.59,4.75]		
5							1.90	[0.51,7.09]		
6							0.68	[0.19,2.41]		
7							7.93	[2.72,23.16]		
8							1.07	[0.28,4.06]		
9							0.52	[0.10,2.72]		
Risk groups										
0000										Ref.
0001										2.04 [0.57,7.37]
0010										2.14 [0.78,5.86]
0011										2.57 [0.62,10.62]
0100										3.39 [0.44,26.24]
0101										5.59 [1.35,23.06]
0110										10.13 [3.30,31.03]
0111										5.00 [1.28,19.55]
1000										1.71 [0.39,7.54]
1001										1.99 [0.23,16.95]
1010										2.70 [0.82,8.89]
1011										3.24 [0.86,12.19]
1100										1.10 [0.13,9.54]
1101										2.03 [0.24,17.47]
1110										7.66 [1.44,40.66]
1111										7.53 [1.70,33.31]
N	4945		4945		4945		4945		4945	
AUC	0.677		0.676		0.646		0.658		0.680	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-2.16: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms on their own, women 50–69

	(1)	(2)	(3)	(4)	(5)
Male					
Female	Ref.	Ref.	Ref.	Ref.	Ref.
White	Ref.	Ref.	Ref.	Ref.	Ref.
Black	1.83 [0.93,3.62]	1.60 [0.81,3.16]	1.51 [0.75,3.04]	1.57 [0.75,3.27]	1.59 [0.79,3.20]
Other	1.60 [0.52,4.93]	1.43 [0.46,4.43]	1.45 [0.49,4.35]	1.40 [0.45,4.38]	1.43 [0.44,4.64]
Age at measurement	0.92 [0.05,16.00]	0.93 [0.05,16.26]	0.78 [0.04,14.96]	0.91 [0.05,16.29]	0.98 [0.05,18.26]
Age^2	1.00 [0.98,1.02]	1.00 [0.98,1.02]	1.00 [0.98,1.03]	1.00 [0.98,1.02]	1.00 [0.98,1.02]
Number of risk factors					
0	Ref.				
1	1.76 [0.65,4.80]				
2	2.44 [0.88,6.78]				
3	4.55 [1.39,14.86]				
4	5.85 [1.00,34.12]				
Risk factors					
High ratio of TC to HDL (>5)		0.99 [0.45,2.16]			
High hbA1c (≥6.4%)		4.76 [2.32,9.78]			
High CRP (≥3.0 ug/mL)		1.27 [0.66,2.43]			
High risk systolic BP (>139)		1.16 [0.58,2.30]			
Continuous biomarkers					
Ratio of TC to HDL			1.05 [0.84,1.32]		
Blood glycated hemoglobin level			1.56 [1.37,1.79]		
Blood CRP level			1.03 [0.92,1.16]		
Systolic BP			1.00 [0.99,1.02]		
Risk profiles					
1				Ref.	
2				0.34 [0.07,1.70]	
3				1.71 [0.47,6.29]	
4				0.80 [0.23,2.85]	
5				1.10 [0.24,5.14]	
6				0.66 [0.18,2.51]	
7				8.34 [2.74,25.39]	
8				1.01 [0.27,3.72]	
9				0.48 [0.09,2.57]	
Risk groups					
0000					Ref.
0001					2.11 [0.61,7.33]
0010					1.31 [0.38,4.55]
0011					0.52 [0.07,3.77]
0100					3.40 [0.43,26.61]
0101					5.85 [1.39,24.55]
0110					9.96 [2.95,33.59]
0111					5.55 [1.06,29.04]
1000					1.79 [0.41,7.87]
1001					2.04 [0.24,17.51]
1010					0.47 [0.06,3.93]
1011					1.90 [0.44,8.17]
1100					1.10 [0.13,9.54]
1101					2.15 [0.25,18.38]
1110					11.19 [1.93,64.94]
1111					5.97 [1.02,35.01]
N	4264	4264	4264	4264	4264
AUC	0.698	0.688	0.678	0.681	0.710

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-2.17: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms on their own, men 70–89

	(1)		(2)		(3)		(4)		(5)	
Male		Ref.		Ref.		Ref.		Ref.		Ref.
Female										
White		Ref.		Ref.		Ref.		Ref.		Ref.
Black	1.26	[0.84,1.89]	1.21	[0.80,1.81]	1.23	[0.82,1.85]	1.21	[0.80,1.82]	1.21	[0.80,1.82]
Other	0.70	[0.27,1.78]	0.68	[0.27,1.75]	0.68	[0.26,1.74]	0.70	[0.27,1.77]	0.68	[0.27,1.72]
Age at measurement	0.60	[0.19,1.93]	0.56	[0.17,1.82]	0.62	[0.19,1.99]	0.58	[0.18,1.89]	0.55	[0.17,1.78]
Age^2	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]
Number of risk factors										
0		Ref.								
1	1.35	[0.96,1.91]								
2	1.23	[0.84,1.80]								
3	1.44	[0.85,2.44]								
4	1.35	[0.37,4.93]								
Risk factors										
High ratio of TC to HDL (>5)			0.81	[0.59,1.13]						
High hbA1c (≥6.4%)			1.22	[0.89,1.66]						
High CRP (≥3.0 ug/mL)			1.59	[1.22,2.06]						
High risk systolic BP (>139)			0.86	[0.66,1.10]						
Continuous biomarkers										
Ratio of TC to HDL					0.92	[0.82,1.04]				
Blood glycated hemoglobin level					1.13	[1.01,1.27]				
Blood CRP level					1.00	[1.00,1.01]				
Systolic BP					1.00	[0.99,1.00]				
Risk profiles										
1								Ref.		
2							1.46	[0.88,2.44]		
3							1.00	[0.58,1.74]		
4							1.33	[0.77,2.28]		
5							1.10	[0.54,2.25]		
6							1.01	[0.60,1.69]		
7							2.26	[1.17,4.37]		
8							0.86	[0.45,1.62]		
9							0.78	[0.44,1.37]		
Risk groups										
0000										Ref.
0001									1.07	[0.70,1.64]
0010									1.90	[1.25,2.89]
0011									1.25	[0.76,2.06]
0100									1.44	[0.77,2.71]
0101									1.03	[0.51,2.06]
0110									2.53	[1.31,4.87]
0111									1.84	[0.80,4.24]
1000									1.07	[0.56,2.04]
1001									0.98	[0.45,2.11]
1010									1.11	[0.51,2.43]
1011									1.31	[0.66,2.61]
1100									0.67	[0.14,3.28]
1101									0.00	[0.00,0.00]
1110									2.25	[0.74,6.82]
1111									1.35	[0.37,4.96]
N	2506		2506		2506		2505		2506	
AUC	0.552		0.586		0.558		0.585		0.590	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-2.18: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms on their own, men 70–89

	(1)		(2)		(3)		(4)		(5)	
Male		Ref.		Ref.		Ref.		Ref.		Ref.
Female										
White		Ref.		Ref.		Ref.		Ref.		Ref.
Black	1.14	[0.72,1.80]	1.11	[0.70,1.75]	1.07	[0.67,1.71]	1.11	[0.70,1.76]	1.10	[0.70,1.75]
Other	0.34	[0.12,0.95]	0.33	[0.12,0.94]	0.34	[0.12,0.96]	0.33	[0.12,0.92]	0.34	[0.12,0.97]
Age at measurement	0.58	[0.16,2.09]	0.54	[0.15,1.94]	0.56	[0.15,2.02]	0.54	[0.15,1.97]	0.53	[0.14,1.93]
Age^2	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]
Number of risk factors										
0		Ref.								
1	1.24	[0.86,1.78]								
2	1.20	[0.80,1.80]								
3	0.97	[0.52,1.81]								
4	1.54	[0.33,7.07]								
Risk factors										
High ratio of TC to HDL (>5)			0.75	[0.51,1.11]						
High hbA1c (≥6.4%)			1.16	[0.81,1.66]						
High CRP (≥3.0 ug/mL)			1.43	[1.06,1.91]						
High risk systolic BP (>139)			0.92	[0.69,1.21]						
Continuous biomarkers										
Ratio of TC to HDL					0.87	[0.76,0.99]				
Blood glycated hemoglobin level					1.13	[0.99,1.30]				
Blood CRP level					1.07	[1.01,1.13]				
Systolic BP					1.00	[0.99,1.01]				
Risk profiles										
1								Ref.		
2							1.18	[0.66,2.11]		
3							1.03	[0.57,1.83]		
4							1.27	[0.71,2.30]		
5							0.76	[0.34,1.69]		
6							1.02	[0.60,1.74]		
7							2.56	[1.23,5.33]		
8							0.87	[0.47,1.62]		
9							0.79	[0.44,1.43]		
Risk groups										
0000										Ref.
0001									1.10	[0.71,1.69]
0010									1.62	[0.99,2.64]
0011									1.29	[0.74,2.25]
0100									1.34	[0.67,2.67]
0101									1.09	[0.54,2.19]
0110									2.80	[1.29,6.05]
0111									1.43	[0.53,3.87]
1000									1.03	[0.51,2.08]
1001									0.91	[0.41,2.02]
1010									1.03	[0.40,2.62]
1011									0.93	[0.39,2.18]
1100									0.65	[0.11,3.80]
1101									0.00	[...]
1110									1.25	[0.28,5.53]
1111									1.54	[0.34,7.11]
N	2165		2165		2165		2164		2165	
AUC	0.551		0.574		0.581		0.576		0.566	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-2.19: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms on their own, women 70–89

	(1)		(2)		(3)		(4)		(5)	
Male										
Female		Ref.		Ref.		Ref.		Ref.		Ref.
White		Ref.		Ref.		Ref.		Ref.		Ref.
Black	1.32	[0.93,1.88]	1.28	[0.89,1.82]	1.26	[0.88,1.82]	1.33	[0.94,1.89]	1.26	[0.87,1.81]
Other	0.70	[0.31,1.58]	0.69	[0.30,1.59]	0.65	[0.30,1.44]	0.69	[0.30,1.61]	0.61	[0.26,1.45]
Age at measurement	1.58	[0.54,4.58]	1.56	[0.54,4.49]	1.57	[0.54,4.53]	1.62	[0.56,4.70]	1.55	[0.53,4.49]
Age^2	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]
Number of risk factors										
0		Ref.								
1	1.14	[0.81,1.62]								
2	1.32	[0.91,1.94]								
3	2.38	[1.55,3.67]								
4	3.61	[1.46,8.91]								
Risk factors										
High ratio of TC to HDL (>5)			1.22	[0.90,1.65]						
High hbA1c (≥6.4%)			1.73	[1.30,2.29]						
High CRP (≥3.0 ug/mL)			1.30	[1.01,1.67]						
High risk systolic BP (>139)			1.17	[0.90,1.50]						
Continuous biomarkers										
Ratio of TC to HDL					1.09	[0.99,1.21]				
Blood glycated hemoglobin level					1.24	[1.12,1.37]				
Blood CRP level					1.01	[1.00,1.02]				
Systolic BP					1.00	[1.00,1.01]				
Risk profiles										
1								Ref.		
2							1.92	[1.16,3.17]		
3							1.44	[0.87,2.37]		
4							1.52	[0.91,2.54]		
5							2.36	[1.23,4.50]		
6							1.23	[0.70,2.14]		
7							2.95	[1.62,5.37]		
8							1.15	[0.64,2.08]		
9							0.93	[0.53,1.61]		
Risk groups										
0000										Ref.
0001									1.01	[0.66,1.55]
0010									1.26	[0.81,1.96]
0011									1.33	[0.80,2.22]
0100									1.57	[0.87,2.84]
0101									1.31	[0.59,2.92]
0110									1.45	[0.68,3.07]
0111									2.92	[1.55,5.48]
1000									1.01	[0.50,2.05]
1001									1.13	[0.52,2.45]
1010									1.26	[0.64,2.48]
1011									1.80	[0.97,3.33]
1100									1.96	[0.67,5.75]
1101									4.41	[1.96,9.95]
1110									1.92	[0.67,5.50]
1111									3.67	[1.48,9.10]
N	3338		3338		3338		3338		3338	
AUC	0.576		0.595		0.585		0.604		0.592	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-2.20: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms on their own, women 70–89

	(1)		(2)		(3)		(4)		(5)	
Male										
Female		Ref.		Ref.		Ref.		Ref.		Ref.
White		Ref.		Ref.		Ref.		Ref.		Ref.
Black	1.30	[0.86,1.97]	1.21	[0.79,1.85]	1.22	[0.81,1.85]	1.31	[0.87,1.97]	1.22	[0.79,1.87]
Other	0.63	[0.24,1.67]	0.60	[0.22,1.66]	0.51	[0.20,1.30]	0.61	[0.22,1.72]	0.52	[0.19,1.48]
Age at measurement	2.06	[0.59,7.16]	2.01	[0.59,6.89]	2.07	[0.60,7.07]	2.13	[0.61,7.40]	2.11	[0.61,7.33]
Age^2	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]
Number of risk factors										
0		Ref.								
1	0.99	[0.67,1.45]								
2	1.16	[0.77,1.75]								
3	2.08	[1.27,3.39]								
4	3.17	[1.07,9.38]								
Risk factors										
High ratio of TC to HDL (>5)			1.11	[0.78,1.58]						
High hbA1c (≥6.4%)			2.01	[1.47,2.74]						
High CRP (≥3.0 ug/mL)			1.11	[0.83,1.48]						
High risk systolic BP (>139)			1.11	[0.83,1.50]						
Continuous biomarkers										
Ratio of TC to HDL					1.07	[0.94,1.21]				
Blood glycated hemoglobin level					1.36	[1.23,1.50]				
Blood CRP level					1.04	[0.98,1.10]				
Systolic BP					1.00	[0.99,1.01]				
Risk profiles										
1								Ref.		
2							1.55	[0.82,2.96]		
3							1.47	[0.84,2.57]		
4							1.35	[0.74,2.46]		
5							2.00	[0.96,4.18]		
6							1.24	[0.70,2.18]		
7							3.73	[1.91,7.30]		
8							1.22	[0.65,2.28]		
9							1.00	[0.56,1.79]		
Risk groups										
0000										Ref.
0001									0.93	[0.58,1.50]
0010									0.96	[0.56,1.62]
0011									1.05	[0.57,1.95]
0100									1.40	[0.75,2.62]
0101									1.33	[0.61,2.90]
0110									1.51	[0.64,3.54]
0111									3.51	[1.76,7.00]
1000									0.93	[0.43,2.01]
1001									1.04	[0.48,2.29]
1010									0.95	[0.40,2.25]
1011									0.90	[0.40,2.03]
1100									1.85	[0.62,5.49]
1101									4.27	[1.82,10.04]
1110									2.21	[0.70,7.03]
1111									3.23	[1.08,9.68]
N	2911		2911		2911		2911		2911	
AUC	0.576		0.589		0.593		0.589		0.585	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.1: Hazard ratios from Cox-models on all-cause mortality with different functional forms conditional on the other forms, total sample

	(1)		(2)		(3)	
Male	Ref.		Ref.		Ref.	
Female	0.63	[0.57,0.70]	0.64	[0.58,0.72]	0.64	[0.58,0.71]
White	Ref.		Ref.		Ref.	
Black	1.17	[1.00,1.37]	1.16	[0.99,1.35]	1.16	[0.99,1.36]
Other	0.81	[0.60,1.08]	0.81	[0.60,1.08]	0.81	[0.60,1.08]
Age at measurement	1.01	[0.81,1.26]	1.00	[0.80,1.25]	1.00	[0.80,1.25]
Age^2	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
Number of risk factors						
0	Ref.					
1	1.32	[1.09,1.59]				
2	1.38	[1.10,1.73]				
3	1.62	[1.20,2.18]				
4	2.37	[1.48,3.79]				
Risk factors						
High ratio of TC to HDL (>5)			0.92	[0.75,1.13]		
High hbA1c (≥6.4%)			1.42	[1.19,1.69]		
High CRP (≥3.0 ug/mL)			1.31	[1.12,1.53]		
High risk systolic BP (>139)			1.02	[0.85,1.22]		
Continuous biomarkers						
Ratio of TC to HDL	0.98	[0.92,1.04]	1.05	[0.97,1.13]	1.05	[0.97,1.13]
Blood glycated hemoglobin level	1.05	[0.98,1.13]	1.01	[0.93,1.10]	1.01	[0.93,1.10]
Blood CRP level	1.01	[1.00,1.01]	1.01	[1.00,1.01]	1.01	[1.00,1.01]
Systolic BP	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	1.55	[1.21,1.99]	1.38	[1.07,1.79]	1.47	[1.12,1.92]
3	1.28	[0.98,1.68]	1.25	[0.95,1.63]	1.26	[0.96,1.65]
4	1.54	[1.22,1.95]	1.42	[1.10,1.83]	1.40	[1.07,1.83]
5	1.39	[0.97,1.98]	1.21	[0.83,1.76]	1.23	[0.84,1.81]
6	0.95	[0.74,1.23]	0.90	[0.69,1.17]	0.93	[0.70,1.22]
7	2.05	[1.43,2.95]	1.77	[1.23,2.53]	1.79	[1.23,2.60]
8	1.19	[0.90,1.56]	1.12	[0.86,1.45]	1.17	[0.89,1.55]
9	0.92	[0.72,1.19]	0.91	[0.71,1.17]	0.92	[0.72,1.19]
Risk groups						
0000					Ref.	
0001					1.19	[0.92,1.52]
0010					1.46	[1.15,1.85]
0011					1.23	[0.92,1.66]
0100					1.46	[1.05,2.01]
0101					1.47	[1.03,2.12]
0110					2.05	[1.46,2.88]
0111					1.80	[1.25,2.58]
1000					0.99	[0.70,1.40]
1001					0.88	[0.56,1.38]
1010					1.28	[0.90,1.82]
1011					1.22	[0.84,1.77]
1100					1.14	[0.69,1.88]
1101					1.57	[0.89,2.76]
1110					1.74	[1.05,2.87]
1111					2.21	[1.37,3.55]
N	14414		14414		14414	
AUC	0.625		0.625		0.626	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.2: Hazard ratios from Cox-models on all-cause mortality with different functional forms conditional on the other forms, total sample

	(1)		(2)		(3)	
Male	Ref.		Ref.		Ref.	
Female	0.63	[0.56,0.70]	0.64	[0.57,0.72]	0.64	[0.57,0.72]
White	Ref.		Ref.		Ref.	
Black	1.20	[1.01,1.43]	1.20	[1.01,1.43]	1.20	[1.01,1.43]
Other	0.85	[0.61,1.18]	0.85	[0.61,1.18]	0.85	[0.61,1.18]
Age at measurement	0.97	[0.75,1.26]	0.97	[0.75,1.25]	0.97	[0.75,1.25]
Age^2	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
Number of risk factors						
0	Ref.					
1	1.12	[0.92,1.36]				
2	0.98	[0.76,1.27]				
3	1.05	[0.75,1.46]				
4	1.25	[0.70,2.22]				
Risk factors						
High ratio of TC to HDL (>5)			0.87	[0.69,1.10]		
High hbA1c (≥6.4%)			1.31	[1.07,1.59]		
High CRP (≥3.0 ug/mL)			0.92	[0.74,1.16]		
High risk systolic BP (>139)			0.96	[0.79,1.17]		
Continuous biomarkers						
Ratio of TC to HDL	1.00	[0.92,1.08]	1.05	[0.96,1.15]	1.04	[0.95,1.15]
Blood glycated hemoglobin level	1.11	[1.03,1.20]	1.05	[0.96,1.15]	1.05	[0.96,1.15]
Blood CRP level	1.09	[1.04,1.13]	1.10	[1.04,1.15]	1.10	[1.04,1.15]
Systolic BP	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	1.28	[0.93,1.75]	1.23	[0.90,1.68]	1.31	[0.94,1.82]
3	1.25	[0.93,1.69]	1.21	[0.90,1.64]	1.24	[0.92,1.68]
4	1.25	[0.95,1.63]	1.27	[0.97,1.67]	1.21	[0.90,1.62]
5	1.19	[0.77,1.83]	1.10	[0.71,1.71]	1.12	[0.70,1.80]
6	1.04	[0.79,1.37]	0.96	[0.72,1.29]	0.98	[0.73,1.32]
7	1.82	[1.17,2.82]	1.67	[1.09,2.55]	1.67	[1.08,2.58]
8	1.21	[0.90,1.62]	1.15	[0.87,1.52]	1.18	[0.88,1.58]
9	1.02	[0.79,1.33]	1.00	[0.77,1.30]	1.01	[0.78,1.31]
Risk groups						
0000					Ref.	
0001					1.09	[0.85,1.41]
0010					1.07	[0.79,1.45]
0011					0.77	[0.53,1.11]
0100					1.30	[0.92,1.84]
0101					1.28	[0.89,1.85]
0110					1.35	[0.89,2.06]
0111					1.22	[0.79,1.87]
1000					0.98	[0.69,1.39]
1001					0.78	[0.50,1.23]
1010					0.87	[0.56,1.35]
1011					0.76	[0.48,1.19]
1100					1.03	[0.61,1.75]
1101					1.41	[0.80,2.48]
1110					0.99	[0.54,1.80]
1111					1.22	[0.69,2.17]
N	12605		12605		12605	
AUC	0.629		0.626		0.629	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.3: Hazard ratios from Cox-models on all-cause mortality with different functional forms conditional on the other forms, men 50–69

	(1)		(2)		(3)	
Male	Ref.		Ref.		Ref.	
Female						
White	Ref.		Ref.		Ref.	
Black	1.43	[0.99,2.08]	1.39	[0.95,2.03]	1.38	[0.94,2.04]
Other	0.93	[0.51,1.71]	0.92	[0.51,1.68]	0.92	[0.50,1.67]
Age at measurement	0.51	[0.16,1.63]	0.51	[0.16,1.64]	0.52	[0.16,1.69]
Age^2	1.01	[1.00,1.01]	1.01	[1.00,1.01]	1.01	[1.00,1.01]
Number of risk factors						
0	Ref.					
1	1.44	[0.83,2.49]				
2	1.45	[0.74,2.84]				
3	1.53	[0.70,3.34]				
4	1.74	[0.38,7.98]				
Risk factors						
High ratio of TC to HDL (>5)			0.63	[0.37,1.07]		
High hbA1c (≥6.4%)			1.54	[0.94,2.53]		
High CRP (≥3.0 ug/mL)			1.40	[0.89,2.22]		
High risk systolic BP (>139)			1.04	[0.67,1.63]		
Continuous biomarkers						
Ratio of TC to HDL	0.98	[0.83,1.14]	1.13	[0.94,1.35]	1.15	[0.95,1.39]
Blood glycated hemoglobin level	1.02	[0.86,1.22]	0.95	[0.78,1.16]	0.96	[0.78,1.18]
Blood CRP level	1.02	[1.01,1.04]	1.02	[1.01,1.03]	1.02	[1.01,1.04]
Systolic BP	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	2.34	[1.09,5.01]	1.92	[0.89,4.16]	2.15	[0.96,4.81]
3	2.14	[0.92,4.97]	2.10	[0.91,4.86]	2.04	[0.88,4.74]
4	2.38	[1.15,4.89]	2.03	[0.94,4.40]	2.09	[0.88,4.96]
5	2.02	[0.80,5.11]	1.76	[0.66,4.73]	1.59	[0.57,4.45]
6	1.68	[0.79,3.57]	1.62	[0.75,3.47]	1.76	[0.80,3.87]
7	2.36	[0.84,6.66]	2.05	[0.78,5.37]	2.00	[0.75,5.36]
8	1.35	[0.56,3.24]	1.13	[0.49,2.60]	1.36	[0.55,3.34]
9	1.17	[0.52,2.60]	1.07	[0.48,2.38]	1.17	[0.52,2.62]
Risk groups						
0000					Ref.	
0001					1.61	[0.84,3.10]
0010					1.67	[0.74,3.75]
0011					1.43	[0.60,3.39]
0100					1.69	[0.68,4.17]
0101					1.92	[0.66,5.57]
0110					3.23	[1.35,7.70]
0111					1.69	[0.58,4.90]
1000					0.71	[0.31,1.64]
1001					0.44	[0.12,1.69]
1010					1.36	[0.50,3.70]
1011					0.97	[0.36,2.61]
1100					0.71	[0.19,2.57]
1101					2.40	[0.78,7.41]
1110					1.38	[0.35,5.39]
1111					1.58	[0.33,7.62]
N	3626		3626		3626	
AUC	0.629		0.635		0.641	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.4: Hazard ratios from Cox-models on all-cause mortality with different functional forms conditional on the other forms, men 50–69

	(1)		(2)		(3)	
Male	Ref.		Ref.		Ref.	
Female						
White	Ref.		Ref.		Ref.	
Black	1.21	[0.79,1.87]	1.20	[0.77,1.86]	1.18	[0.75,1.85]
Other	1.02	[0.54,1.94]	1.00	[0.53,1.88]	0.99	[0.52,1.86]
Age at measurement	0.56	[0.16,1.97]	0.53	[0.15,1.87]	0.53	[0.15,1.92]
Age^2	1.00	[0.99,1.02]	1.01	[1.00,1.02]	1.01	[0.99,1.02]
Number of risk factors						
0	Ref.					
1	1.21	[0.68,2.14]				
2	0.70	[0.34,1.45]				
3	0.83	[0.35,1.98]				
4	0.63	[0.11,3.72]				
Risk factors						
High ratio of TC to HDL (> 5)			0.57	[0.32,1.03]		
High hbA1c (≥ 6.4%)			1.42	[0.82,2.45]		
High CRP (≥ 3.0 ug/mL)			0.62	[0.31,1.21]		
High risk systolic BP (> 139)			1.02	[0.62,1.66]		
Continuous biomarkers						
Ratio of TC to HDL	1.02	[0.85,1.23]	1.15	[0.94,1.42]	1.16	[0.92,1.46]
Blood glycated hemoglobin level	1.12	[0.92,1.36]	1.01	[0.80,1.28]	1.01	[0.80,1.28]
Blood CRP level	1.21	[1.08,1.36]	1.26	[1.09,1.46]	1.27	[1.11,1.47]
Systolic BP	1.01	[1.00,1.02]	1.01	[0.99,1.02]	1.01	[0.99,1.02]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	1.59	[0.62,4.04]	1.49	[0.58,3.80]	1.69	[0.63,4.50]
3	2.11	[0.88,5.06]	1.97	[0.83,4.68]	1.96	[0.82,4.71]
4	1.50	[0.62,3.59]	1.73	[0.71,4.18]	1.55	[0.57,4.18]
5	1.63	[0.58,4.62]	1.53	[0.52,4.52]	1.50	[0.47,4.79]
6	1.90	[0.89,4.05]	1.79	[0.83,3.84]	1.91	[0.87,4.19]
7	1.35	[0.37,4.95]	1.24	[0.38,4.03]	1.22	[0.38,3.95]
8	1.46	[0.60,3.58]	1.27	[0.55,2.97]	1.50	[0.62,3.63]
9	1.50	[0.64,3.49]	1.40	[0.61,3.23]	1.53	[0.66,3.54]
Risk groups						
0000					Ref.	
0001					1.50	[0.77,2.96]
0010					0.90	[0.34,2.38]
0011					0.48	[0.16,1.43]
0100					1.70	[0.67,4.29]
0101					1.80	[0.62,5.24]
0110					1.20	[0.36,4.00]
0111					0.56	[0.15,2.12]
1000					0.70	[0.29,1.69]
1001					0.32	[0.08,1.38]
1010					0.41	[0.13,1.28]
1011					0.49	[0.16,1.54]
1100					0.65	[0.17,2.41]
1101					2.13	[0.69,6.60]
1110					0.44	[0.06,3.39]
1111					0.52	[0.09,3.10]
N	3266		3266		3266	
AUC	0.618		0.626		0.633	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.5: Hazard ratios from Cox-models on all-cause mortality with different functional forms conditional on the other forms, women 50-69

	(1)		(2)		(3)	
Male						
Female	Ref.		Ref.		Ref.	
White	Ref.		Ref.		Ref.	
Black	1.11	[0.61,2.04]	1.15	[0.63,2.08]	1.11	[0.61,2.02]
Other	1.06	[0.39,2.88]	1.06	[0.39,2.91]	1.10	[0.40,3.03]
Age at measurement	0.34	[0.04,3.08]	0.33	[0.04,3.04]	0.33	[0.04,3.02]
Age^2	1.01	[0.99,1.03]	1.01	[0.99,1.03]	1.01	[0.99,1.03]
Number of risk factors						
0	Ref.					
1	1.81	[0.68,4.80]				
2	2.62	[0.84,8.20]				
3	2.17	[0.47,9.96]				
4	2.46	[0.29,20.75]				
Risk factors						
High ratio of TC to HDL (>5)			0.91	[0.33,2.49]		
High hbA1c (≥6.4%)			1.38	[0.61,3.15]		
High CRP (≥3.0 ug/mL)			1.22	[0.63,2.38]		
High risk systolic BP (>139)			1.84	[0.60,5.65]		
Continuous biomarkers						
Ratio of TC to HDL	1.07	[0.81,1.42]	1.16	[0.83,1.63]	1.16	[0.82,1.63]
Blood glycated hemoglobin level	1.13	[0.86,1.48]	1.09	[0.79,1.50]	1.13	[0.81,1.57]
Blood CRP level	1.02	[1.02,1.03]	1.02	[1.02,1.03]	1.02	[1.02,1.03]
Systolic BP	1.00	[0.98,1.02]	0.99	[0.96,1.02]	0.99	[0.97,1.02]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	0.73	[0.21,2.57]	0.80	[0.22,2.84]	0.83	[0.23,3.02]
3	1.22	[0.30,5.07]	1.43	[0.36,5.66]	1.28	[0.29,5.71]
4	1.15	[0.36,3.61]	1.26	[0.41,3.84]	1.54	[0.43,5.59]
5	0.75	[0.14,3.91]	0.83	[0.15,4.65]	0.86	[0.13,5.56]
6	0.46	[0.11,1.89]	0.55	[0.13,2.34]	0.56	[0.11,2.82]
7	2.83	[0.56,14.25]	3.05	[0.64,14.45]	2.91	[0.55,15.52]
8	1.29	[0.29,5.82]	1.08	[0.25,4.69]	1.43	[0.28,7.28]
9	0.69	[0.13,3.51]	0.59	[0.11,3.17]	0.68	[0.13,3.50]
Risk groups						
0000					Ref.	
0001					3.28	[0.56,19.12]
0010					1.39	[0.56,3.41]
0011					3.17	[0.55,18.13]
0100					2.02	[0.26,15.79]
0101					4.50	[0.73,27.69]
0110					3.15	[0.98,10.11]
0111					2.53	[0.38,17.01]
1000					1.65	[0.28,9.68]
1001					2.33	[0.16,34.45]
1010					1.71	[0.42,6.98]
1011					3.23	[0.53,19.86]
1100					0.72	[0.06,9.03]
1101					1.64	[0.13,21.15]
1110					1.56	[0.19,13.08]
1111					2.69	[0.34,21.40]
N	4945		4945		4945	
AUC	0.667		0.670		0.675	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.6: Hazard ratios from Cox-models on all-cause mortality with different functional forms conditional on the other forms, women 50–69

	(1)		(2)		(3)	
Male						
Female	Ref.		Ref.		Ref.	
White	Ref.		Ref.		Ref.	
Black	1.41	[0.90,2.19]	1.39	[0.89,2.17]	1.36	[0.86,2.13]
Other	0.80	[0.38,1.69]	0.80	[0.38,1.70]	0.82	[0.38,1.75]
Age at measurement	0.85	[0.20,3.53]	0.83	[0.20,3.41]	0.83	[0.20,3.44]
Age^2	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Number of risk factors						
0	Ref.					
1	1.32	[0.73,2.37]				
2	1.61	[0.75,3.48]				
3	1.75	[0.58,5.30]				
4	1.76	[0.34,9.11]				
Risk factors						
High ratio of TC to HDL (>5)			0.77	[0.38,1.57]		
High hbA1c (≥6.4%)			1.70	[0.98,2.94]		
High CRP (≥3.0 ug/mL)			1.15	[0.61,2.16]		
High risk systolic BP (>139)			1.45	[0.74,2.83]		
Continuous biomarkers						
Ratio of TC to HDL	1.01	[0.80,1.28]	1.14	[0.87,1.49]	1.16	[0.87,1.54]
Blood glycated hemoglobin level	1.04	[0.84,1.29]	0.98	[0.77,1.25]	1.00	[0.78,1.28]
Blood CRP level	1.07	[0.97,1.18]	1.08	[0.96,1.22]	1.09	[0.96,1.23]
Systolic BP	0.99	[0.98,1.01]	0.99	[0.98,1.01]	0.99	[0.98,1.01]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	0.62	[0.24,1.57]	0.62	[0.25,1.54]	0.60	[0.23,1.60]
3	1.31	[0.46,3.72]	1.33	[0.49,3.62]	1.37	[0.48,3.97]
4	0.78	[0.37,1.62]	0.77	[0.36,1.64]	0.75	[0.34,1.68]
5	0.54	[0.15,1.95]	0.56	[0.15,2.19]	0.46	[0.12,1.85]
6	0.49	[0.20,1.18]	0.50	[0.20,1.25]	0.48	[0.18,1.23]
7	2.18	[0.71,6.69]	1.90	[0.65,5.54]	1.68	[0.56,5.08]
8	0.88	[0.37,2.08]	0.82	[0.35,1.91]	0.80	[0.32,1.98]
9	0.66	[0.27,1.64]	0.64	[0.26,1.58]	0.64	[0.26,1.61]
Risk groups						
0000					Ref.	
0001					1.54	[0.63,3.79]
0010					1.17	[0.53,2.59]
0011					1.44	[0.43,4.75]
0100					1.77	[0.55,5.65]
0101					3.89	[1.37,11.09]
0110					2.22	[0.83,5.92]
0111					3.24	[0.87,12.03]
1000					0.97	[0.35,2.69]
1001					0.79	[0.07,8.77]
1010					1.12	[0.37,3.38]
1011					1.22	[0.25,5.93]
1100					0.26	[0.03,2.24]
1101					1.19	[0.20,7.22]
1110					1.32	[0.23,7.55]
1111					1.86	[0.38,9.20]
N	4264		4264		4264	
AUC	0.634		0.642		0.647	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.7: Hazard ratios from Cox-models on all-cause mortality with different functional forms conditional on the other forms, men 70-89

	(1)		(2)		(3)	
Male	Ref.		Ref.		Ref.	
Female						
White	Ref.		Ref.		Ref.	
Black	1.07	[0.83,1.39]	1.06	[0.82,1.37]	1.07	[0.83,1.38]
Other	0.84	[0.49,1.42]	0.83	[0.49,1.42]	0.82	[0.49,1.39]
Age at measurement	0.90	[0.44,1.85]	0.90	[0.44,1.84]	0.90	[0.44,1.84]
Age^2	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]
Number of risk factors						
0	Ref.					
1	1.35	[1.02,1.78]				
2	1.25	[0.88,1.78]				
3	1.57	[1.00,2.47]				
4	1.64	[0.68,3.96]				
Risk factors						
High ratio of TC to HDL (>5)			1.02	[0.73,1.43]		
High hbA1c (≥6.4%)			1.20	[0.91,1.58]		
High CRP (≥3.0 ug/mL)			1.40	[1.09,1.80]		
High risk systolic BP (>139)			0.86	[0.65,1.12]		
Continuous biomarkers						
Ratio of TC to HDL	0.89	[0.80,0.98]	0.91	[0.80,1.04]	0.91	[0.79,1.04]
Blood glycated hemoglobin level	1.01	[0.89,1.15]	1.01	[0.87,1.16]	1.01	[0.87,1.16]
Blood CRP level	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Systolic BP	1.00	[0.99,1.00]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	2.09	[1.45,3.00]	1.73	[1.18,2.54]	1.80	[1.21,2.67]
3	1.26	[0.84,1.91]	1.22	[0.81,1.85]	1.20	[0.78,1.85]
4	1.52	[1.05,2.19]	1.30	[0.89,1.91]	1.24	[0.83,1.85]
5	1.90	[1.10,3.28]	1.53	[0.87,2.67]	1.67	[0.93,3.03]
6	0.97	[0.66,1.43]	0.93	[0.63,1.37]	0.92	[0.62,1.38]
7	2.39	[1.34,4.27]	1.88	[1.04,3.41]	1.90	[1.01,3.60]
8	1.36	[0.89,2.07]	1.25	[0.84,1.87]	1.33	[0.87,2.03]
9	0.93	[0.64,1.37]	0.94	[0.64,1.37]	0.95	[0.65,1.39]
Risk groups						
0000					Ref.	
0001					1.01	[0.70,1.46]
0010					1.72	[1.21,2.45]
0011					1.10	[0.70,1.72]
0100					1.30	[0.80,2.11]
0101					1.08	[0.63,1.84]
0110					1.75	[0.98,3.12]
0111					1.79	[1.06,3.04]
1000					1.29	[0.75,2.20]
1001					1.04	[0.55,1.96]
1010					1.32	[0.71,2.44]
1011					1.32	[0.72,2.39]
1100					1.34	[0.60,3.01]
1101					0.57	[0.14,2.43]
1110					1.85	[0.81,4.20]
1111					1.52	[0.62,3.70]
N	2505		2505		2505	
AUC	0.634		0.642		0.647	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.8: Hazard ratios from Cox-models on all-cause mortality with different functional forms conditional on the other forms, men 70–89

	(1)		(2)		(3)	
Male	Ref.		Ref.		Ref.	
Female						
White	Ref.		Ref.		Ref.	
Black	1.18	[0.91,1.55]	1.18	[0.91,1.55]	1.19	[0.91,1.56]
Other	0.73	[0.40,1.32]	0.72	[0.39,1.31]	0.73	[0.40,1.33]
Age at measurement	0.78	[0.35,1.72]	0.76	[0.35,1.68]	0.76	[0.34,1.69]
Age^2	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]
Number of risk factors						
0	Ref.					
1	1.23	[0.92,1.65]				
2	1.18	[0.79,1.75]				
3	1.17	[0.69,1.96]				
4	1.38	[0.45,4.20]				
Risk factors						
High ratio of TC to HDL (>5)			0.95	[0.66,1.38]		
High hbA1c (≥6.4%)			1.18	[0.85,1.62]		
High CRP (≥3.0 ug/mL)			1.32	[0.93,1.86]		
High risk systolic BP (>139)			0.88	[0.65,1.18]		
Continuous biomarkers						
Ratio of TC to HDL	0.89	[0.79,1.00]	0.91	[0.79,1.06]	0.91	[0.78,1.05]
Blood glycated hemoglobin level	1.03	[0.89,1.18]	0.99	[0.85,1.17]	1.00	[0.85,1.17]
Blood CRP level	1.04	[0.99,1.11]	1.01	[0.94,1.08]	1.01	[0.94,1.08]
Systolic BP	1.00	[0.99,1.00]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	1.77	[1.14,2.73]	1.60	[1.02,2.49]	1.69	[1.07,2.68]
3	1.22	[0.77,1.92]	1.18	[0.75,1.87]	1.16	[0.72,1.86]
4	1.34	[0.88,2.05]	1.25	[0.82,1.91]	1.21	[0.76,1.92]
5	1.80	[0.98,3.31]	1.61	[0.86,3.01]	1.74	[0.87,3.49]
6	1.05	[0.70,1.57]	0.99	[0.65,1.50]	0.98	[0.64,1.49]
7	2.47	[1.26,4.83]	2.20	[1.13,4.30]	2.12	[1.05,4.27]
8	1.36	[0.87,2.13]	1.25	[0.81,1.92]	1.34	[0.85,2.10]
9	1.03	[0.69,1.53]	0.97	[0.65,1.45]	0.99	[0.66,1.47]
Risk groups						
0000					Ref.	
0001					1.02	[0.70,1.49]
0010					1.57	[1.00,2.46]
0011					1.09	[0.63,1.88]
0100					1.26	[0.75,2.13]
0101					1.07	[0.60,1.89]
0110					1.95	[1.00,3.81]
0111					1.67	[0.90,3.13]
1000					1.25	[0.70,2.21]
1001					0.99	[0.50,1.94]
1010					1.28	[0.60,2.71]
1011					1.04	[0.51,2.13]
1100					1.38	[0.60,3.20]
1101					0.58	[0.14,2.31]
1110					1.34	[0.51,3.49]
1111					1.44	[0.46,4.50]
N	2164		2164		2164	
AUC	0.602		0.604		0.607	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.9: Hazard ratios from Cox-models on all-cause mortality with different functional forms conditional on the other forms, women 70–89

	(1)		(2)		(3)	
Male						
Female	Ref.		Ref.		Ref.	
White	Ref.		Ref.		Ref.	
Black	0.98	[0.76,1.26]	0.98	[0.76,1.26]	0.97	[0.76,1.25]
Other	0.76	[0.45,1.26]	0.78	[0.47,1.30]	0.74	[0.44,1.24]
Age at measurement	1.31	[0.67,2.56]	1.32	[0.68,2.57]	1.32	[0.68,2.57]
Age^2	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]
Number of risk factors						
0	Ref.					
1	1.08	[0.83,1.41]				
2	1.08	[0.78,1.49]				
3	1.21	[0.78,1.88]				
4	2.20	[1.14,4.25]				
Risk factors						
High ratio of TC to HDL (>5)			1.13	[0.84,1.52]		
High hbA1c (≥6.4%)			1.35	[1.02,1.79]		
High CRP (≥3.0 ug/mL)			1.03	[0.82,1.29]		
High risk systolic BP (>139)			0.95	[0.71,1.26]		
Continuous biomarkers						
Ratio of TC to HDL	1.03	[0.93,1.14]	1.04	[0.92,1.18]	1.04	[0.92,1.17]
Blood glycated hemoglobin level	1.15	[1.03,1.29]	1.11	[0.98,1.26]	1.10	[0.97,1.25]
Blood CRP level	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Systolic BP	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	1.47	[1.00,2.16]	1.44	[0.97,2.14]	1.46	[0.97,2.20]
3	1.14	[0.78,1.66]	1.07	[0.73,1.58]	1.13	[0.76,1.67]
4	1.60	[1.10,2.32]	1.60	[1.08,2.37]	1.49	[0.99,2.23]
5	1.22	[0.64,2.33]	1.08	[0.55,2.11]	1.23	[0.63,2.40]
6	0.91	[0.59,1.40]	0.79	[0.50,1.26]	0.78	[0.49,1.26]
7	1.64	[0.93,2.91]	1.54	[0.88,2.71]	1.62	[0.90,2.90]
8	1.15	[0.74,1.78]	1.12	[0.73,1.72]	1.10	[0.70,1.71]
9	0.92	[0.64,1.33]	0.91	[0.63,1.31]	0.90	[0.62,1.31]
Risk groups						
0000					Ref.	
0001					0.93	[0.64,1.36]
0010					1.14	[0.81,1.61]
0011					0.90	[0.57,1.41]
0100					1.28	[0.82,2.00]
0101					1.17	[0.66,2.07]
0110					1.26	[0.73,2.18]
0111					1.17	[0.66,2.07]
1000					1.10	[0.67,1.83]
1001					0.96	[0.52,1.77]
1010					0.93	[0.54,1.59]
1011					1.10	[0.63,1.92]
1100					2.05	[0.95,4.42]
1101					1.70	[0.77,3.77]
1110					1.09	[0.46,2.60]
1111					2.23	[1.15,4.31]
N	3338		3338		3338	
AUC	0.598		0.602		0.604	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.10: Hazard ratios from Cox-models on all-cause mortality with different functional forms conditional on the other forms, women 70–89

	(1)		(2)		(3)	
Male						
Female	Ref.		Ref.		Ref.	
White	Ref.		Ref.		Ref.	
Black	1.02	[0.77,1.36]	1.01	[0.76,1.35]	1.02	[0.76,1.37]
Other	0.69	[0.38,1.24]	0.73	[0.41,1.29]	0.69	[0.39,1.22]
Age at measurement	1.47	[0.70,3.07]	1.45	[0.69,3.04]	1.46	[0.70,3.07]
Age^2	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]
Number of risk factors						
0	Ref.					
1	0.95	[0.71,1.26]				
2	0.88	[0.60,1.30]				
3	0.95	[0.56,1.61]				
4	1.32	[0.56,3.10]				
Risk factors						
High ratio of TC to HDL (>5)			1.12	[0.79,1.60]		
High hbA1c (≥6.4%)			1.25	[0.92,1.68]		
High CRP (≥3.0 ug/mL)			0.76	[0.53,1.08]		
High risk systolic BP (>139)			0.89	[0.65,1.23]		
Continuous biomarkers						
Ratio of TC to HDL	1.09	[0.97,1.21]	1.08	[0.94,1.23]	1.07	[0.93,1.23]
Blood glycated hemoglobin level	1.25	[1.11,1.41]	1.21	[1.06,1.37]	1.17	[1.02,1.33]
Blood CRP level	1.05	[0.98,1.12]	1.09	[1.00,1.18]	1.09	[1.00,1.19]
Systolic BP	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	1.10	[0.67,1.81]	1.08	[0.66,1.76]	1.10	[0.65,1.85]
3	1.14	[0.73,1.76]	1.07	[0.69,1.66]	1.13	[0.73,1.77]
4	1.35	[0.90,2.05]	1.38	[0.90,2.12]	1.30	[0.83,2.02]
5	0.89	[0.42,1.88]	0.80	[0.37,1.72]	0.81	[0.36,1.80]
6	0.86	[0.55,1.33]	0.73	[0.45,1.19]	0.76	[0.46,1.25]
7	1.33	[0.69,2.56]	1.25	[0.66,2.38]	1.40	[0.72,2.74]
8	1.05	[0.68,1.63]	1.05	[0.68,1.63]	1.03	[0.66,1.61]
9	0.94	[0.62,1.42]	0.96	[0.63,1.44]	0.96	[0.63,1.45]
Risk groups						
0000					Ref.	
0001					0.88	[0.60,1.30]
0010					0.82	[0.52,1.29]
0011					0.60	[0.33,1.07]
0100					1.10	[0.68,1.77]
0101					1.10	[0.61,1.96]
0110					0.65	[0.33,1.31]
0111					0.99	[0.49,1.96]
1000					1.05	[0.57,1.91]
1001					0.88	[0.46,1.69]
1010					0.86	[0.44,1.67]
1011					0.63	[0.31,1.28]
1100					1.76	[0.75,4.12]
1101					1.51	[0.67,3.40]
1110					0.99	[0.39,2.55]
1111					1.36	[0.59,3.16]
N	2911		2911		2911	
AUC	0.590		0.598		0.600	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.11: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms conditional on the other forms, total sample

	(1)		(2)		(3)	
Male	Ref.		Ref.		Ref.	
Female	0.68	[0.58,0.81]	0.71	[0.60,0.84]	0.70	[0.59,0.83]
White	Ref.		Ref.		Ref.	
Black	1.22	[0.96,1.55]	1.20	[0.95,1.53]	1.20	[0.95,1.53]
Other	0.81	[0.51,1.29]	0.81	[0.51,1.30]	0.81	[0.51,1.30]
Age at measurement	1.26	[0.87,1.81]	1.25	[0.86,1.80]	1.24	[0.86,1.79]
Age^2	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
Number of risk factors						
0	Ref.					
1	1.39	[1.02,1.88]				
2	1.34	[0.92,1.96]				
3	1.62	[1.02,2.58]				
4	2.04	[0.91,4.55]				
Risk factors						
High ratio of TC to HDL (>5)			0.80	[0.57,1.13]		
High hbA1c (≥6.4%)			1.34	[1.01,1.77]		
High CRP (≥3.0 ug/mL)			1.31	[1.03,1.67]		
High risk systolic BP (>139)			1.08	[0.80,1.46]		
Continuous biomarkers						
Ratio of TC to HDL	0.97	[0.88,1.07]	1.07	[0.95,1.20]	1.06	[0.94,1.20]
Blood glycated hemoglobin level	1.17	[1.05,1.29]	1.14	[1.01,1.28]	1.15	[1.03,1.29]
Blood CRP level	1.01	[1.00,1.01]	1.01	[1.00,1.01]	1.01	[1.00,1.01]
Systolic BP	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	1.54	[1.04,2.27]	1.34	[0.91,1.99]	1.42	[0.94,2.14]
3	1.27	[0.84,1.91]	1.24	[0.82,1.86]	1.19	[0.79,1.81]
4	1.37	[0.94,2.01]	1.28	[0.85,1.92]	1.29	[0.83,2.01]
5	1.69	[0.96,2.98]	1.50	[0.84,2.69]	1.64	[0.89,3.02]
6	0.95	[0.64,1.41]	0.93	[0.61,1.40]	0.93	[0.60,1.44]
7	1.91	[1.06,3.45]	1.64	[0.93,2.89]	1.57	[0.86,2.84]
8	1.25	[0.78,1.99]	1.15	[0.74,1.79]	1.24	[0.77,2.00]
9	0.95	[0.64,1.41]	0.95	[0.64,1.40]	0.96	[0.64,1.42]
Risk groups						
0000					Ref.	
0001					1.33	[0.88,2.00]
0010					1.48	[0.99,2.19]
0011					1.40	[0.87,2.27]
0100					1.58	[0.95,2.65]
0101					1.12	[0.62,2.05]
0110					2.28	[1.32,3.94]
0111					1.77	[0.98,3.18]
1000					0.98	[0.54,1.78]
1001					0.97	[0.51,1.86]
1010					0.93	[0.51,1.69]
1011					1.22	[0.70,2.14]
1100					0.80	[0.33,1.92]
1101					1.46	[0.66,3.24]
1110					1.61	[0.70,3.69]
1111					1.80	[0.79,4.09]
N	14414		14414		14414	
AUC	0.631		0.629		0.632	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.12: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms conditional on the other forms, total sample

	(1)		(2)		(3)	
Male	Ref.		Ref.		Ref.	
Female	0.67	[0.56,0.81]	0.69	[0.57,0.84]	0.69	[0.57,0.83]
White	Ref.		Ref.		Ref.	
Black	1.17	[0.90,1.52]	1.17	[0.90,1.52]	1.15	[0.89,1.50]
Other	0.74	[0.42,1.29]	0.74	[0.42,1.30]	0.75	[0.43,1.31]
Age at measurement	1.45	[0.94,2.24]	1.44	[0.93,2.22]	1.43	[0.92,2.21]
Age^2	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
Number of risk factors						
0	Ref.					
1	1.24	[0.89,1.72]				
2	1.03	[0.68,1.56]				
3	1.30	[0.77,2.20]				
4	1.67	[0.68,4.10]				
Risk factors						
High ratio of TC to HDL (>5)			0.95	[0.84,1.07]		
High hbA1c (≥6.4%)			1.19	[1.06,1.33]		
High CRP (≥3.0 ug/mL)			1.05	[0.99,1.12]		
High risk systolic BP (>139)			1.00	[0.99,1.01]		
Continuous biomarkers						
Ratio of TC to HDL	0.95	[0.84,1.07]	1.03	[0.89,1.19]	1.01	[0.87,1.17]
Blood glycated hemoglobin level	1.19	[1.06,1.33]	1.14	[1.00,1.30]	1.16	[1.02,1.32]
Blood CRP level	1.05	[0.99,1.12]	1.04	[0.95,1.13]	1.03	[0.94,1.12]
Systolic BP	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	1.24	[0.75,2.05]	1.15	[0.70,1.87]	1.31	[0.79,2.18]
3	1.38	[0.88,2.17]	1.31	[0.83,2.06]	1.32	[0.83,2.09]
4	1.01	[0.64,1.60]	1.01	[0.64,1.60]	0.95	[0.57,1.58]
5	1.58	[0.86,2.90]	1.40	[0.75,2.61]	1.71	[0.89,3.26]
6	1.05	[0.69,1.60]	0.96	[0.62,1.48]	0.98	[0.62,1.55]
7	2.23	[1.14,4.35]	1.92	[1.02,3.65]	1.86	[0.97,3.58]
8	1.28	[0.80,2.05]	1.20	[0.76,1.89]	1.25	[0.78,2.01]
9	1.02	[0.68,1.55]	1.00	[0.66,1.51]	0.99	[0.65,1.51]
Risk groups						
0000					Ref.	
0001					1.17	[0.77,1.78]
0010					1.40	[0.82,2.38]
0011					0.97	[0.54,1.75]
0100					1.35	[0.78,2.35]
0101					0.98	[0.53,1.80]
0110					1.98	[1.02,3.83]
0111					1.65	[0.83,3.27]
1000					1.01	[0.54,1.89]
1001					0.90	[0.46,1.78]
1010					0.67	[0.32,1.37]
1011					0.79	[0.40,1.57]
1100					0.76	[0.30,1.93]
1101					1.40	[0.61,3.22]
1110					1.60	[0.65,3.93]
1111					1.60	[0.66,3.90]
N	12605		12605		12605	
AUC	0.629		0.626		0.629	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.13: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms conditional on the other forms, men 50–69

	(1)		(2)		(3)	
Male	Ref.		Ref.		Ref.	
Female						
White	Ref.		Ref.		Ref.	
Black	1.29	[0.66,2.52]	1.19	[0.59,2.40]	1.16	[0.57,2.37]
Other	0.84	[0.31,2.31]	0.82	[0.31,2.17]	0.82	[0.31,2.15]
Age at measurement	1.86	[0.18,19.08]	2.01	[0.17,23.54]	2.20	[0.18,27.20]
Age^2	1.00	[0.98,1.01]	1.00	[0.98,1.02]	0.99	[0.97,1.01]
Number of risk factors						
0	Ref.					
1	4.94	[1.67,14.66]				
2	5.98	[1.63,21.99]				
3	6.09	[1.46,25.45]				
4	8.31	[1.05,65.79]				
Risk factors						
High ratio of TC to HDL (>5)			0.32	[0.10,1.07]		
High hbA1c (≥6.4%)			2.34	[1.04,5.27]		
High CRP (≥3.0 ug/mL)			2.55	[1.17,5.54]		
High risk systolic BP (>139)			1.30	[0.57,2.98]		
Continuous biomarkers						
Ratio of TC to HDL	1.04	[0.83,1.30]	1.39	[1.06,1.81]	1.40	[1.05,1.87]
Blood glycated hemoglobin level	1.23	[0.98,1.55]	1.10	[0.85,1.43]	1.14	[0.90,1.43]
Blood CRP level	1.03	[1.01,1.05]	1.02	[1.00,1.04]	1.02	[1.00,1.04]
Systolic BP	1.00	[0.98,1.02]	1.00	[0.98,1.03]	1.00	[0.98,1.03]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	2.26	[0.60,8.57]	1.55	[0.44,5.46]	1.75	[0.52,5.81]
3	1.30	[0.29,5.87]	1.35	[0.29,6.33]	1.24	[0.27,5.69]
4	1.70	[0.43,6.66]	1.22	[0.30,5.00]	1.16	[0.25,5.47]
5	1.83	[0.43,7.70]	1.78	[0.38,8.37]	2.09	[0.46,9.45]
6	0.70	[0.18,2.78]	0.75	[0.19,2.98]	0.82	[0.20,3.34]
7	1.54	[0.27,8.93]	1.30	[0.27,6.17]	1.34	[0.28,6.47]
8	3.97	[0.82,19.11]	2.12	[0.48,9.33]	4.35	[0.89,21.20]
9	2.28	[0.55,9.38]	1.74	[0.40,7.62]	2.40	[0.54,10.76]
Risk groups						
0000					Ref.	
0001					5.53	[1.46,20.90]
0010					7.88	[1.83,33.90]
0011					8.89	[1.82,43.39]
0100					7.28	[1.44,36.81]
0101					4.74	[0.74,30.27]
0110					24.44	[5.25,113.72]
0111					10.58	[1.98,56.70]
1000					1.19	[0.15,9.45]
1001					0.93	[0.07,12.75]
1010					1.70	[0.22,13.21]
1011					1.89	[0.30,11.82]
1100					0.00	[.,.]
1101					4.89	[0.61,39.31]
1110					3.68	[0.32,42.36]
1111					5.36	[0.58,49.61]
N	3626		3626		3626	
AUC	0.716		0.718		0.720	

Note: 95%-CI in brackets. Individuals with CRP ≥10 $\frac{mg}{l}$ excluded.

Table A-3.14: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms conditional on the other forms, men 50-69

	(1)		(2)		(3)	
Male	Ref.		Ref.		Ref.	
Female						
White	Ref.		Ref.		Ref.	
Black	0.85	[0.44,1.66]	0.79	[0.40,1.59]	0.74	[0.36,1.52]
Other	0.78	[0.25,2.41]	0.75	[0.25,2.28]	0.72	[0.23,2.21]
Age at measurement	1.07	[0.07,15.64]	1.07	[0.07,16.79]	1.14	[0.07,18.81]
Age^2	1.00	[0.98,1.02]	1.00	[0.98,1.02]	1.00	[0.98,1.02]
Number of risk factors						
0	Ref.					
1	4.33	[1.50,12.50]				
2	2.20	[0.55,8.69]				
3	3.45	[0.73,16.31]				
4	3.79	[0.36,40.01]				
Risk factors						
High ratio of TC to HDL (>5)			0.46	[0.14,1.56]		
High hbA1c (≥6.4%)			2.62	[1.12,6.15]		
High CRP (≥3.0 ug/mL)			1.54	[0.50,4.74]		
High risk systolic BP (>139)			0.95	[0.38,2.39]		
Continuous biomarkers						
Ratio of TC to HDL	0.85	[0.44,1.66]	0.79	[0.40,1.59]	0.74	[0.36,1.52]
Blood glycated hemoglobin level	0.78	[0.25,2.41]	0.75	[0.25,2.28]	0.72	[0.23,2.21]
Blood CRP level	1.07	[0.07,15.64]	1.07	[0.07,16.79]	1.14	[0.07,18.81]
Systolic BP	1.00	[0.98,1.02]	1.00	[0.98,1.02]	1.00	[0.98,1.02]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	1.43	[0.30,6.74]	1.11	[0.23,5.32]	1.32	[0.31,5.59]
3	1.61	[0.37,7.12]	1.53	[0.33,7.12]	1.46	[0.30,7.05]
4	0.35	[0.04,3.21]	0.34	[0.04,3.03]	0.22	[0.02,2.26]
5	2.10	[0.52,8.48]	1.60	[0.34,7.51]	2.05	[0.45,9.28]
6	0.91	[0.22,3.84]	0.74	[0.19,2.88]	0.78	[0.19,3.27]
7	1.49	[0.21,10.38]	0.98	[0.19,5.10]	1.02	[0.20,5.32]
8	4.35	[0.96,19.84]	2.32	[0.54,9.93]	3.83	[0.88,16.70]
9	3.08	[0.70,13.58]	2.08	[0.46,9.40]	2.75	[0.59,12.73]
Risk groups						
0000					Ref.	
0001					3.69	[0.99,13.81]
0010					7.59	[1.69,33.99]
0011					1.89	[0.27,13.04]
0100					7.41	[1.44,38.17]
0101					3.84	[0.60,24.58]
0110					13.29	[2.01,87.82]
0111					5.76	[0.86,38.74]
1000					1.44	[0.17,12.26]
1001					0.90	[0.06,13.62]
1010					1.08	[0.14,8.30]
1011					1.38	[0.21,9.14]
1100					0.02	[0.00,1.87e+08]
1101					5.22	[0.73,37.21]
1110					3.49	[0.27,44.94]
1111					3.80	[0.42,34.19]
N	3266		3266		3266	
AUC	0.716		0.716		0.721	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.15: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms conditional on the other forms, women 50–69

	(1)		(2)		(3)	
Male						
Female	Ref.		Ref.		Ref.	
White	Ref.		Ref.		Ref.	
Black	1.24	[0.87,1.79]	1.24	[0.87,1.78]	1.21	[0.84,1.74]
Other	0.70	[0.37,1.33]	0.70	[0.37,1.33]	0.71	[0.37,1.35]
Age at measurement	0.85	[0.26,2.76]	0.84	[0.26,2.72]	0.85	[0.26,2.75]
Age^2	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Number of risk factors						
0	Ref.					
1	1.57	[0.95,2.61]				
2	2.48	[1.32,4.63]				
3	2.63	[1.08,6.38]				
4	4.86	[1.61,14.71]				
Risk factors						
High ratio of TC to HDL (>5)			0.90	[0.51,1.57]		
High hbA1c (≥6.4%)			1.92	[1.19,3.11]		
High CRP (≥3.0 ug/mL)			1.53	[1.01,2.31]		
High risk systolic BP (>139)			1.68	[0.94,2.98]		
Continuous biomarkers						
Ratio of TC to HDL	1.03	[0.87,1.23]	1.18	[0.96,1.45]	1.19	[0.96,1.48]
Blood glycated hemoglobin level	1.01	[0.84,1.21]	0.95	[0.77,1.17]	0.95	[0.77,1.19]
Blood CRP level	1.02	[1.01,1.02]	1.02	[1.01,1.02]	1.02	[1.01,1.02]
Systolic BP	0.99	[0.98,1.00]	0.99	[0.98,1.00]	0.99	[0.98,1.00]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	0.74	[0.35,1.56]	0.72	[0.33,1.55]	0.75	[0.34,1.68]
3	1.28	[0.52,3.14]	1.31	[0.54,3.17]	1.39	[0.56,3.44]
4	1.04	[0.55,1.96]	1.01	[0.51,2.02]	1.03	[0.49,2.15]
5	0.72	[0.27,1.90]	0.69	[0.24,1.96]	0.63	[0.22,1.81]
6	0.40	[0.17,0.95]	0.42	[0.18,1.02]	0.44	[0.18,1.09]
7	1.94	[0.78,4.83]	1.70	[0.67,4.32]	1.67	[0.63,4.40]
8	0.86	[0.37,2.01]	0.81	[0.35,1.86]	0.84	[0.34,2.07]
9	0.66	[0.28,1.55]	0.64	[0.27,1.51]	0.66	[0.27,1.59]
Risk groups						
0000					Ref.	
0001					1.90	[0.79,4.54]
0010					1.55	[0.88,2.73]
0011					2.66	[1.08,6.55]
0100					2.22	[0.71,6.90]
0101					5.85	[2.09,16.38]
0110					3.30	[1.48,7.37]
0111					4.60	[1.58,13.34]
1000					0.96	[0.37,2.52]
1001					1.03	[0.09,11.46]
1010					1.78	[0.82,3.88]
1011					1.78	[0.46,6.87]
1100					0.34	[0.04,2.93]
1101					1.60	[0.25,10.25]
1110					2.37	[0.74,7.65]
1111					5.04	[1.71,14.82]
N	4945		4945		4945	
AUC	0.684		0.681		0.690	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.16: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms conditional on the other forms, women 50–69

	(1)		(2)		(3)	
Male						
Female	Ref.		Ref.		Ref.	
White	Ref.		Ref.		Ref.	
Black	1.44	[0.69,2.97]	1.45	[0.71,2.94]	1.43	[0.69,2.94]
Other	1.35	[0.43,4.24]	1.37	[0.44,4.25]	1.43	[0.44,4.60]
Age at measurement	0.92	[0.05,17.45]	0.88	[0.05,15.89]	0.91	[0.05,17.84]
Age^2	1.00	[0.98,1.02]	1.00	[0.98,1.02]	1.00	[0.98,1.03]
Number of risk factors						
0	Ref.					
1	1.77	[0.53,5.89]				
2	1.88	[0.42,8.52]				
3	2.84	[0.40,20.32]				
4	1.76	[0.11,28.74]				
Risk factors						
High ratio of TC to HDL (>5)			0.95	[0.25,3.59]		
High hbA1c (≥6.4%)			1.90	[0.69,5.19]		
High CRP (≥3.0 ug/mL)			1.38	[0.45,4.26]		
High risk systolic BP (>139)			1.13	[0.32,4.00]		
Continuous biomarkers						
Ratio of TC to HDL	1.04	[0.76,1.42]	1.13	[0.75,1.70]	1.12	[0.75,1.68]
Blood glycated hemoglobin level	1.14	[0.83,1.56]	1.10	[0.78,1.56]	1.16	[0.82,1.63]
Blood CRP level	0.98	[0.83,1.16]	0.97	[0.77,1.23]	0.97	[0.77,1.22]
Systolic BP	1.00	[0.98,1.03]	1.00	[0.97,1.03]	1.01	[0.97,1.04]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	0.23	[0.04,1.35]	0.23	[0.04,1.33]	0.29	[0.05,1.76]
3	1.19	[0.27,5.31]	1.23	[0.27,5.52]	1.14	[0.23,5.73]
4	0.81	[0.20,3.31]	0.78	[0.21,2.94]	0.88	[0.23,3.44]
5	0.74	[0.13,4.16]	0.69	[0.11,4.47]	1.03	[0.14,7.72]
6	0.50	[0.12,2.12]	0.47	[0.10,2.17]	0.50	[0.09,2.71]
7	3.75	[0.52,27.01]	2.76	[0.49,15.62]	2.28	[0.36,14.66]
8	1.27	[0.29,5.56]	1.10	[0.26,4.60]	1.34	[0.28,6.46]
9	0.57	[0.11,3.05]	0.52	[0.09,2.88]	0.54	[0.11,2.77]
Risk groups						
0000					Ref.	
0001					1.93	[0.33,11.50]
0010					1.62	[0.38,6.88]
0011					0.69	[0.07,6.95]
0100					1.77	[0.21,15.12]
0101					2.47	[0.36,16.80]
0110					4.52	[0.85,24.19]
0111					2.86	[0.24,34.18]
1000					1.70	[0.24,12.05]
1001					1.45	[0.08,24.61]
1010					0.53	[0.05,5.12]
1011					2.59	[0.27,24.96]
1100					0.70	[0.05,10.79]
1101					0.95	[0.06,14.24]
1110					4.17	[0.40,43.90]
1111					1.89	[0.14,25.20]
N	4264		4264		4264	
AUC	0.703		0.702		0.726	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.17: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms conditional on the other forms, men 70–89

	(1)		(2)		(3)	
Male	Ref.		Ref.		Ref.	
Female						
White	Ref.		Ref.		Ref.	
Black	1.19	[0.79,1.80]	1.15	[0.76,1.75]	1.16	[0.76,1.77]
Other	0.69	[0.27,1.76]	0.69	[0.27,1.76]	0.67	[0.26,1.69]
Age at measurement	0.58	[0.18,1.87]	0.58	[0.18,1.88]	0.57	[0.18,1.85]
Age^2	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]
Number of risk factors						
0	Ref.					
1	1.30	[0.86,1.97]				
2	1.06	[0.60,1.88]				
3	1.28	[0.59,2.76]				
4	1.35	[0.32,5.81]				
Risk factors						
High ratio of TC to HDL (>5)			1.05	[0.61,1.81]		
High hbA1c (≥6.4%)			0.95	[0.58,1.55]		
High CRP (≥3.0 ug/mL)			1.35	[0.90,2.01]		
High risk systolic BP (>139)			0.81	[0.53,1.25]		
Continuous biomarkers						
Ratio of TC to HDL	0.81	[0.68,0.96]	0.81	[0.66,1.01]	0.81	[0.65,1.00]
Blood glycated hemoglobin level	0.97	[0.80,1.17]	1.01	[0.81,1.25]	1.02	[0.82,1.28]
Blood CRP level	1.00	[0.99,1.01]	0.99	[0.98,1.00]	0.99	[0.98,1.00]
Systolic BP	0.99	[0.98,1.00]	1.00	[0.98,1.01]	1.00	[0.99,1.01]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	2.03	[1.11,3.70]	1.67	[0.90,3.10]	1.82	[0.95,3.51]
3	1.53	[0.80,2.91]	1.52	[0.79,2.93]	1.46	[0.74,2.90]
4	1.25	[0.69,2.29]	1.10	[0.59,2.04]	1.05	[0.54,2.02]
5	2.26	[0.93,5.49]	1.76	[0.71,4.33]	2.11	[0.78,5.71]
6	1.33	[0.73,2.41]	1.32	[0.72,2.43]	1.33	[0.70,2.51]
7	3.15	[1.19,8.32]	2.46	[0.92,6.63]	2.37	[0.81,6.97]
8	0.90	[0.43,1.88]	0.84	[0.42,1.69]	0.92	[0.44,1.92]
9	0.81	[0.45,1.45]	0.82	[0.46,1.47]	0.84	[0.47,1.51]
Risk groups						
0000					Ref.	
0001					1.01	[0.58,1.74]
0010					1.70	[0.98,2.97]
0011					0.92	[0.44,1.92]
0100					1.11	[0.51,2.38]
0101					0.79	[0.32,1.94]
0110					1.47	[0.56,3.87]
0111					1.11	[0.41,3.04]
1000					1.26	[0.56,2.83]
1001					1.15	[0.45,2.94]
1010					1.09	[0.37,3.23]
1011					1.28	[0.48,3.41]
1100					0.68	[0.12,3.79]
1101					0.00	[0.00,0.00]
1110					1.99	[0.55,7.24]
1111					1.22	[0.28,5.30]
N	2505		2505		2505	
AUC	0.602		0.602		0.607	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.18: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms conditional on the other forms, men 70–89

	(1)		(2)		(3)	
Male	Ref.		Ref.		Ref.	
Female						
White	Ref.		Ref.		Ref.	
Black	1.07	[0.67,1.72]	1.05	[0.65,1.69]	1.05	[0.65,1.70]
Other	0.33	[0.12,0.94]	0.32	[0.11,0.93]	0.33	[0.11,0.94]
Age at measurement	0.55	[0.15,1.99]	0.55	[0.15,1.95]	0.54	[0.15,1.96]
Age^2	1.00	[1.00,1.01]	1.00	[1.00,1.01]	1.00	[1.00,1.01]
Number of risk factors						
0	Ref.					
1	1.22	[0.77,1.92]				
2	1.13	[0.60,2.12]				
3	0.94	[0.39,2.25]				
4	1.85	[0.31,10.91]				
Risk factors						
High ratio of TC to HDL (>5)			1.08	[0.60,1.94]		
High hbA1c (≥6.4%)			0.82	[0.47,1.42]		
High CRP (≥3.0 ug/mL)			1.48	[0.81,2.70]		
High risk systolic BP (>139)			0.91	[0.57,1.46]		
Continuous biomarkers						
Ratio of TC to HDL	0.78	[0.64,0.95]	0.77	[0.60,0.98]	0.76	[0.60,0.98]
Blood glycated hemoglobin level	0.93	[0.75,1.15]	0.99	[0.78,1.25]	1.00	[0.79,1.28]
Blood CRP level	1.02	[0.93,1.11]	0.96	[0.86,1.08]	0.96	[0.85,1.07]
Systolic BP	0.99	[0.98,1.01]	1.00	[0.98,1.01]	1.00	[0.98,1.01]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	1.69	[0.84,3.41]	1.48	[0.71,3.10]	1.61	[0.74,3.54]
3	1.55	[0.76,3.16]	1.55	[0.75,3.20]	1.52	[0.72,3.21]
4	1.18	[0.60,2.30]	1.10	[0.56,2.16]	1.07	[0.51,2.26]
5	1.72	[0.60,4.92]	1.51	[0.51,4.48]	1.60	[0.43,5.96]
6	1.52	[0.79,2.93]	1.56	[0.79,3.05]	1.52	[0.75,3.06]
7	4.22	[1.47,12.09]	3.93	[1.31,11.77]	3.70	[1.15,11.88]
8	0.99	[0.48,2.06]	0.92	[0.45,1.88]	0.99	[0.48,2.07]
9	0.87	[0.47,1.61]	0.83	[0.45,1.53]	0.83	[0.45,1.55]
Risk groups						
0000					Ref.	
0001					1.05	[0.60,1.86]
0010					1.75	[0.80,3.83]
0011					1.25	[0.51,3.08]
0100					0.96	[0.41,2.23]
0101					0.79	[0.30,2.05]
0110					1.71	[0.55,5.29]
0111					0.98	[0.30,3.21]
1000					1.34	[0.56,3.17]
1001					1.22	[0.46,3.23]
1010					1.59	[0.35,7.12]
1011					1.40	[0.40,4.88]
1100					0.64	[0.10,4.24]
1101					0.00	[.,.]
1110					1.36	[0.24,7.73]
1111					2.13	[0.34,13.45]
N	2164		2164		2164	
AUC	0.599		0.601		0.594	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.19: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms conditional on the other forms, women 70–89

	(1)		(2)		(3)	
Male						
Female	Ref.		Ref.		Ref.	
White	Ref.		Ref.		Ref.	
Black	1.24	[0.86,1.78]	1.23	[0.86,1.77]	1.21	[0.84,1.75]
Other	0.62	[0.28,1.36]	0.63	[0.27,1.43]	0.58	[0.25,1.34]
Age at measurement	1.61	[0.55,4.66]	1.63	[0.56,4.75]	1.61	[0.55,4.72]
Age^2	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]
Number of risk factors						
0	Ref.					
1	0.97	[0.64,1.47]				
2	0.93	[0.55,1.58]				
3	1.31	[0.68,2.52]				
4	1.62	[0.56,4.69]				
Risk factors						
High ratio of TC to HDL (>5)			1.03	[0.65,1.62]		
High hbA1c (≥6.4%)			1.33	[0.89,2.00]		
High CRP (≥3.0 ug/mL)			0.93	[0.65,1.34]		
High risk systolic BP (>139)			1.16	[0.75,1.80]		
Continuous biomarkers						
Ratio of TC to HDL	1.00	[0.85,1.17]	1.03	[0.86,1.24]	1.04	[0.86,1.25]
Blood glycated hemoglobin level	1.23	[1.04,1.44]	1.19	[0.99,1.43]	1.18	[0.98,1.44]
Blood CRP level	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Systolic BP	1.00	[0.99,1.01]	1.00	[0.99,1.01]	1.00	[0.99,1.01]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	1.64	[0.93,2.91]	1.73	[0.96,3.13]	1.63	[0.90,2.95]
3	1.25	[0.68,2.30]	1.20	[0.66,2.20]	1.28	[0.69,2.37]
4	1.67	[0.94,2.95]	1.82	[0.98,3.36]	1.73	[0.91,3.30]
5	2.05	[0.80,5.29]	2.02	[0.76,5.37]	2.17	[0.80,5.88]
6	1.13	[0.60,2.14]	1.03	[0.52,2.02]	0.97	[0.48,1.97]
7	1.16	[0.47,2.88]	1.22	[0.51,2.94]	1.18	[0.48,2.91]
8	1.24	[0.60,2.53]	1.30	[0.64,2.65]	1.16	[0.56,2.44]
9	0.94	[0.52,1.70]	0.95	[0.53,1.72]	0.91	[0.50,1.67]
Risk groups						
0000					Ref.	
0001					1.00	[0.56,1.79]
0010					0.87	[0.50,1.52]
0011					1.03	[0.53,2.02]
0100					1.36	[0.70,2.64]
0101					0.92	[0.35,2.41]
0110					0.91	[0.39,2.16]
0111					1.59	[0.69,3.64]
1000					0.93	[0.41,2.13]
1001					0.89	[0.34,2.32]
1010					0.67	[0.30,1.51]
1011					1.12	[0.50,2.50]
1100					1.54	[0.44,5.35]
1101					2.22	[0.75,6.54]
1110					0.77	[0.19,3.06]
1111					1.65	[0.56,4.91]
N	3338		3338		3338	
AUC	0.610		0.613		0.611	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.

Table A-3.20: Hazard ratios from Cox-models on CVD-cause mortality with different functional forms conditional on the other forms, women 70–89

	(1)		(2)		(3)	
Male						
Female	Ref.		Ref.		Ref.	
White	Ref.		Ref.		Ref.	
Black	1.23	[0.81,1.87]	1.21	[0.80,1.85]	1.22	[0.79,1.87]
Other	0.50	[0.21,1.21]	0.52	[0.20,1.37]	0.49	[0.19,1.26]
Age at measurement	2.21	[0.64,7.67]	2.23	[0.65,7.72]	2.28	[0.65,7.96]
Age^2	1.00	[0.99,1.00]	1.00	[0.99,1.00]	1.00	[0.99,1.00]
Number of risk factors						
0	Ref.					
1	0.89	[0.56,1.41]				
2	0.87	[0.48,1.56]				
3	1.27	[0.60,2.71]				
4	1.39	[0.39,4.99]				
Risk factors						
High ratio of TC to HDL (>5)			0.89	[0.51,1.56]		
High hbA1c (≥6.4%)			1.46	[0.94,2.28]		
High CRP (≥3.0 ug/mL)			0.78	[0.44,1.39]		
High risk systolic BP (>139)			1.17	[0.72,1.91]		
Continuous biomarkers						
Ratio of TC to HDL	1.00	[0.84,1.20]	1.07	[0.87,1.32]	1.07	[0.86,1.33]
Blood glycated hemoglobin level	1.36	[1.13,1.62]	1.27	[1.03,1.56]	1.25	[1.00,1.55]
Blood CRP level	1.00	[0.90,1.10]	1.05	[0.92,1.19]	1.05	[0.91,1.20]
Systolic BP	1.00	[0.99,1.01]	1.00	[0.98,1.01]	1.00	[0.98,1.01]
Risk profiles						
1	Ref.		Ref.		Ref.	
2	1.33	[0.61,2.89]	1.35	[0.63,2.91]	1.27	[0.58,2.79]
3	1.51	[0.76,2.97]	1.43	[0.74,2.77]	1.53	[0.78,3.01]
4	1.30	[0.65,2.61]	1.40	[0.67,2.93]	1.40	[0.64,3.03]
5	1.63	[0.58,4.59]	1.57	[0.54,4.57]	1.66	[0.52,5.28]
6	1.01	[0.52,1.95]	0.90	[0.44,1.83]	0.90	[0.44,1.88]
7	1.17	[0.44,3.13]	1.22	[0.47,3.16]	1.19	[0.46,3.11]
8	1.07	[0.51,2.26]	1.18	[0.55,2.52]	1.06	[0.49,2.29]
9	0.93	[0.49,1.76]	1.00	[0.53,1.91]	0.97	[0.50,1.87]
Risk groups						
0000					Ref.	
0001					0.98	[0.52,1.84]
0010					0.64	[0.28,1.48]
0011					0.88	[0.37,2.05]
0100					1.13	[0.57,2.22]
0101					0.98	[0.39,2.51]
0110					0.81	[0.28,2.32]
0111					2.01	[0.78,5.19]
1000					0.83	[0.31,2.20]
1001					0.82	[0.31,2.18]
1010					0.48	[0.16,1.42]
1011					0.56	[0.20,1.57]
1100					1.34	[0.35,5.11]
1101					2.16	[0.71,6.59]
1110					0.88	[0.21,3.66]
1111					1.31	[0.36,4.77]
N	2911		2911		2911	
BIC	0.605		0.610		0.609	

Note: 95%-CI in brackets. Individuals with CRP ≥ 10 $\frac{mg}{l}$ excluded.