



Review Article

Predictive value of traditional risk factors for cardiovascular disease in older people: A systematic review



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ABSTRACT

With increasing age, associations between traditional risk factors (TRFs) and cardiovascular disease (CVD) shift. It is unknown which mid-life risk factors remain relevant predictors for CVD in older people.

We systematically searched PubMed and EMBASE on August 16th 2019 for studies assessing predictive ability of > 1 of fourteen TRFs for fatal and non-fatal CVD, in the general population aged 60+.

We included 12 studies, comprising 11 unique cohorts. TRF were evaluated in 2 to 11 cohorts, and retained in 0–70% of the cohorts: age (70%), diabetes (64%), male sex (57%), systolic blood pressure (SBP) (50%), smoking (36%), high-density lipoprotein cholesterol (HDL) (33%), left ventricular hypertrophy (LVH) (33%), total cholesterol (22%), diastolic blood pressure (20%), antihypertensive medication use (AHM) (20%), body mass index (BMI) (0%), hypertension (0%), low-density lipoprotein cholesterol (0%). In studies with low to moderate risk of bias, systolic blood pressure (SBP) (80%), smoking (80%) and HDL cholesterol (60%) were more often retained. Model performance was moderate with C-statistics ranging from 0.61 to 0.77.

Compared to middle-aged adults, in people aged 60+ different risk factors predict CVD and current prediction models perform only moderate at best. According to most studies, age, sex and diabetes seem valuable predictors of CVD in old-age. SBP, HDL cholesterol and smoking may also have predictive value. Other blood pressure and cholesterol related variables, BMI, and LVH seem of very limited or no additional value. Without competing risk analysis, predictors are overestimated.

1. Introduction

Improvements in cardiovascular disease (CVD) prevention have contributed to a decline in cardiovascular mortality since the 1980s (Nichols et al., 2014). However, CVD remains a major cause of disability and mortality, especially among older individuals (Timmis et al., 2018). Timely identification of people at increased risk is required to target effective preventive interventions to the right persons, thereby improving CVD prevention. CVD risk may be estimated using prediction

models (Piepoli et al., 2016). Decades of research in middle-aged individuals has created strong evidence supporting the value of traditional risk factors (TRFs) including age, sex, systolic blood pressure (SBP), diabetes mellitus (DM), smoking, and total cholesterol (TC), for predicting CVD in midlife.

However, associations between TRFs and CVD seem to attenuate with increasing age (sometimes referred to as ‘reversed epidemiology’) (Ahmadi et al., 2015; Hamer et al., 2009; Koller et al., 2012a). Models developed in middle-aged persons perform poorly in older populations

Abbreviations: AHM, antihypertensive medication; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; LVH, left ventricular hypertrophy; PROBAST, Prediction model Risk Of Bias ASessment Tool; SBP, systolic blood pressure; TC, total cholesterol; TRF, traditional risk factor

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(Hamer et al., 2009; Koller et al., 2012a). Studies and clinical guidelines often assume that mid-life risk factors are similarly applicable in old-age, while it would be more appropriate to develop risk prediction models specifically for older people (Cooney et al., 2016; de Ruijter et al., 2009; Stork et al., 2006).

Although the pathophysiology underlying CVD is thought to be similar in middle and old-age, it is unclear which mid-life TRFs are useful predictors for CVD in older people (Cooney et al., 2016; de Ruijter et al., 2009). Currently, there appears to be a paucity of evidence, with only few studies specifically addressing CVD risk prediction in older people (Damen et al., 2016).

With this systematic literature review, we aim to collate and synthesize the evidence on the predictive value of traditional risk factors in persons aged 60 years and over.

2. Methods

2.1. Search strategy and procedures

We included fourteen TRFs that are commonly reported in well-known midlife prediction models: age, sex, race, body mass index (BMI), SBP, diastolic blood pressure (DPB), hypertension, anti-hypertensive medication use (AHM), DM, smoking, TC, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), and left ventricular hypertrophy (LVH). (Anderson et al., 1991; Conroy et al., 2003; D'Agostino Sr. et al., 2008; Hippisley-Cox et al., 2010) We searched for studies that evaluated the predictive value of at least two TRFs for first incident CVD in people aged 60 or older, in population based longitudinal cohorts or registry data. The outcome had to be fatal or non-fatal coronary heart disease (CHD), non-CHD CVD or all CVD (further referred to as CVD).

Predictive ability of variables had to be evaluated through prediction-model development by univariable and/or multivariable model selection procedures. PRISMA reporting guidelines were followed (Liberati et al., 2009), and the protocol was published in PROSPERO on January 31, 2019 (Van Bussel et al., 2019b) [<https://www.crd.york.ac.uk/PROSPERO>, registration number CRD42019103004].

We conducted a systematic literature search in PubMed and EMBASE on August 16, 2019. The search syntax was developed in collaboration with a clinical librarian, and included synonyms and MeSH/Emtree terms for 'CVD' and 'older persons' and synonyms for 'prediction' (see Table S1 for full syntax). The search was limited to humans, English language and articles published since 1998, since interest for and research into CVD prediction models for older people mostly started after this date (Anderson et al., 1991; Damen et al., 2016). Results were deduplicated in EndNote X8.2. Titles and abstracts, and full-texts of potentially relevant articles, were independently screened by two authors (MH, EB) using predefined in- and exclusion criteria (Box S1). Reference lists and citations of the included articles were searched to identify additional potentially relevant studies.

2.2. Data extraction

The list of extracted items was based on the Cochrane guidance for data extraction and critical appraisal for systematic reviews of prediction models (CHARMS checklist) (Moons et al., 2014), supplemented by items obtained from a recent systematic review on this topic (Damen et al., 2016). The full list can be found in the study protocol (Van Bussel et al., 2019b). Two reviewers (EB, MH) extracted data independently. Discrepancies were resolved through discussion (with a third author (EMC)). In case of missing information study authors were contacted.

2.3. Quality assessment

Risk of bias (ROB) was assessed using the 'Prediction model Risk Of Bias Assessment Tool' (PROBAST), which comprises 19 signalling

questions to facilitate structured judgment of the ROB in four domains: participants, predictors, outcomes and analysis (Moons et al., 2019). Based on these questions, overall ROB and concerns regarding applicability were assessed. The rationale for the bias score for each domain is provided in text S1.

Study screening, data extraction and quality assessment were performed independently by two authors (MH, EB). Disagreements were resolved by discussion, with involvement of a third reviewer (EMC) if necessary. Since MH, EB and EMC were involved in one of the included studies, RP and JG assessed its quality (van Bussel et al., 2019c).

2.4. Statistical analyses

Risk factors were considered 'retained' either if they were included in the final CVD prediction model following an algorithmic selection procedure or were forced in and significantly predicted the outcome.

For retained risk factors, the effect sizes were extracted and standardized, synchronizing reference groups and units. When only *p*-values were reported, 95% confidence intervals (95%CI) were calculated (Altman and Bland, 2011). Next, meta-analyses were performed for each retained TRF. When effect sizes were given for men and women separately, both were included in the meta-analyses. When results were reported for CHD and non-CHD CVD, results were pooled and the resulting effect size was included in the meta-analyses. Statistical analyses were performed using the "meta" package in R 3.5.1 (Schwarzer, 2007).

2.5. Subgroup and sensitivity analyses

Subgroup analyses were performed for different outcomes, by sex, low vs high ROB and the subgroup without any form of CVD at baseline. Subgroup analyses for frailty and age groups (dichotomized at 80 years) were predefined in the protocol but could not be performed due to insufficient data.

Since blood pressure related variables show high collinearity, they tend to compete with each other in models when added to the same backward selection procedure. The same is true for and cholesterol related variables. Therefore, all blood pressure related variables (SBP, DBP, hypertension and AHM) and all cholesterol related variables (TC, HDL and LDL) were combined into the umbrella terms 'blood pressure' and 'cholesterol' respectively. When one or more of the variables were retained in a model, the umbrella term was counted as retained.

CVD, cardiovascular disease; TRF, traditional risk factors.

3. Results

After screening 8745 abstracts, 85 full-texts were evaluated, eventually yielding 12 relevant articles, reporting on 11 unique cohorts (Fig. 1). Two articles reporting different outcomes (CHD and non-CHD CVD) from the Cardiovascular Health Study cohort, were both included (Lumley et al., 2002; Psaty et al., 1999). Reference screening yielded no additional relevant studies.

3.1. Characteristics of studies

Cohorts originated from Europe ($n = 6$), North America ($n = 2$) and Australia ($n = 3$). Mean baseline age ranged from 69 to 85 years. Outcome events were identified from health records and/or death certificates ($n = 6$), self-report verified by health records ($n = 2$), a combination of self-report and health records, or diagnosed by a panel ($n = 2$). Outcome events were fatal ($n = 5$) or combined fatal and non-fatal ($n = 6$) CHD, non-CHD CVD, or CVD. Studies had a median of 1957 (range 302 to 40,825) participants and 290 (range 28 to 4144) outcome events. The median follow-up duration was 6.5 (range 4 to 12) years. All study cohorts were population based. Study details are given in Table 1.

Included studies evaluated four to 11 TRFs for CVD. Most studies

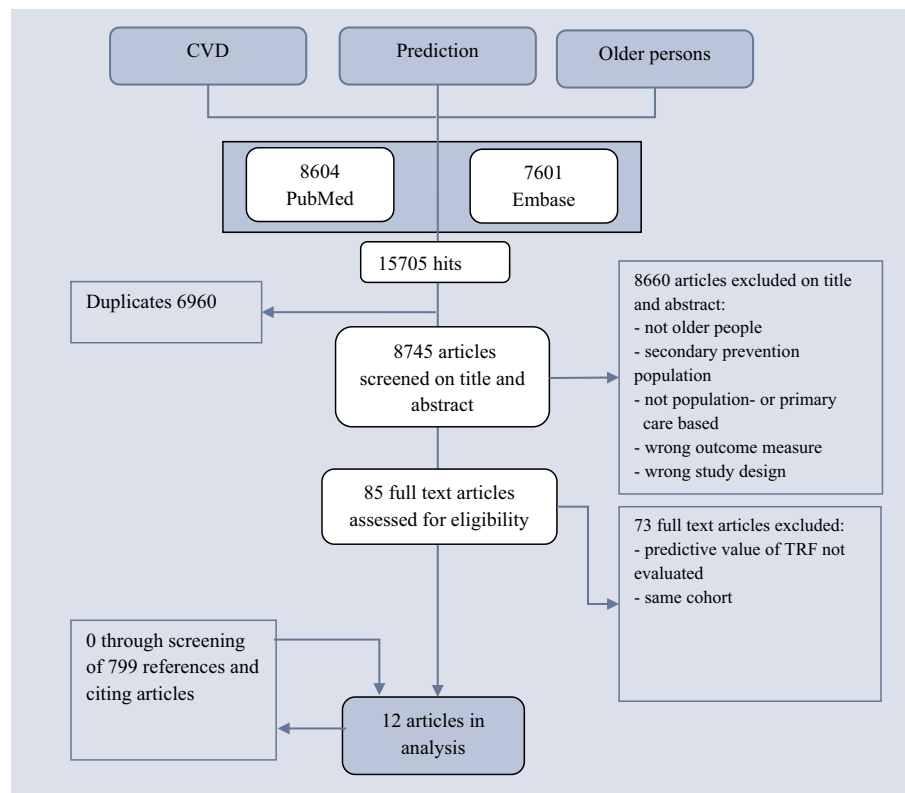


Fig. 1. Flow diagram of selected articles for predictors for CVD in older persons. August 16, 2019.

evaluated the predictive performance of component variables of well-known prediction models (e.g. Framingham, SCORE). Other motivations for evaluated risk factors were generally not given. Two studies did not evaluate age and sex since their cohort consisted of participants all aged 85 years (de Ruijter et al., 2009) or men only (Beer et al., 2011), respectively. Three studies stratified by sex, and thus did not evaluate sex as a predictor (Ahto et al., 2007; Cooney et al., 2016; Noto et al., 2002).

All information in this table applies to the (sub) analyses of individual studies that are appropriate for this systematic review. Studies are chronologically ordered based on baseline year.

3.2. Quality assessment

For the 12 selected studies, overall risk of bias was rated low for one, moderate for five, and high for six (Table 2 and S2). All studies had low risk of bias in the ‘participants’ and ‘predictors’ domains of the quality assessment, meaning that participants were recruited using appropriate data sources and inclusion criteria, and definitions and assessment of the evaluated predictors were adequate and similar for all participants. In the ‘outcome’ domain, risk of bias was high for one study because one evaluated predictor (hypertension) also featured prominently in the fatal CVD outcome (hypertension as cause of death in 8/28 = 29% of cases) (Muscari et al., 2013). In the ‘analysis’ domain, risk of bias was low for one, moderate for five, and high for six studies. The most common source of bias was inappropriate handling of complexities in the data ($n = 11$): two studies did not use survival analyses for longitudinal data (Noto et al., 2002; Simons et al., 2003), and all but one accounted for competing risks. (van Bussel et al., 2019c) Other common sources of bias in analyses included absence of adjustment for overfitting ($n = 11$) (Ahto et al., 2007; Beer et al., 2011; Cooney et al., 2016; Jamrozik et al., 2000; Lumley et al., 2002; Muscari et al., 2013; Noto et al., 2002; Psaty et al., 1999; Rodondi et al., 2012; de Ruijter et al., 2009; Simons et al., 2003) and optimism in model performance

($n = 10$) (Ahto et al., 2007; Beer et al., 2011; Cooney et al., 2016; Jamrozik et al., 2000; Lumley et al., 2002; Muscari et al., 2013; Noto et al., 2002; Psaty et al., 1999; de Ruijter et al., 2009; Simons et al., 2003), excluding cases with missing values when multiple imputation would have been preferable ($n = 10$) (Ahto et al., 2007; Beer et al., 2011; Cooney et al., 2016; Jamrozik et al., 2000; Muscari et al., 2013; Noto et al., 2002; Psaty et al., 1999; Rodondi et al., 2012; de Ruijter et al., 2009; Simons et al., 2003), and not reporting any calibration or discrimination measures ($n = 6$) (Ahto et al., 2007; Jamrozik et al., 2000; Muscari et al., 2013; Noto et al., 2002; Psaty et al., 1999; Simons et al., 2003) or only a measure for discrimination ($n = 2$) (Lumley et al., 2002; Rodondi et al., 2012). Uncommon sources of bias were few outcome events compared to the number of variables tested ($n = 5$) (Ahto et al., 2007; Jamrozik et al., 2000; Muscari et al., 2013; Noto et al., 2002; de Ruijter et al., 2009), categorization of continuous predictors, reducing their predictive value ($n = 4$) (Ahto et al., 2007; Beer et al., 2011; Muscari et al., 2013; Noto et al., 2002), and exclusion of > 20% of the original population ($n = 1$) (Beer et al., 2011), or not reporting numbers excluded from the analyses ($n = 3$) (Noto et al., 2002; Psaty et al., 1999; Simons et al., 2003). Finally, two studies did not follow fully appropriate predictor selection procedures, because variables were not tested individually (de Ruijter et al., 2009), or only univariable analysis was used (Ahto et al., 2007).

Overall, the applicability of the studies to the research question of this review was rated high for all studies except for four. In three studies, this was due to risk of bias in the ‘participants’ domain because of only excluding participants with selected CVDs that were similar to the outcome, but not all forms of CVD (Ahto et al., 2007; Cooney et al., 2016; Lumley et al., 2002). In the other, this was due to high risk of bias in the ‘outcome’ domain because the predictor ‘hypertension’ also featured prominently in the fatal CVD outcome (Muscari et al., 2013). (Table 2).

Table 1
Characteristics of included studies.

| Author (year) | Continent | Study period | Study design | Cohort name | No. of participants | Population age (years) | Sex (% men) | Follow-up duration | Inclusion criteria | Sampling | Outcome | No. of outcome events |
|---------------------------|---------------|--------------------|--|--|---------------------|----------------------------------|--------------|-------------------------------|--|--|---------------------------------|-----------------------|
| Cooney et al. (2016) | Europe | 1977–2003 | Prospective cohorts | SCORE (BIRNH, Glostrup, RIFLE) and CONOR | 40,825 | Median 72; range 65–101 | 55% | Median 6.8–7.8 year | Free of CHD | 4 prospective population based cohorts from Belgium, Denmark, Italy and Norway | Fatal CHD and fatal non-CHD CVD | 4144 |
| Simons et al. (2003) | Australia | Baseline 1988 | Prospective cohort | Dubbo | 2102 | Mean 69; range ≥ 60 | 42% | Study duration 10 year | Free of CVD, non-institutionalized, born before 1930 | All residents of the semi-urban town Dubbo, born < 1930 were invited | Fatal or non-fatal CVD | ca 438 |
| Psaty et al. (1999) | North America | Baseline 1989–1993 | Prospective cohort, augmented after 2y with more African Americans | Cardiovascular health study | 4037 | Mean 73, range ≥ 65 | 40% | Mean 4.8 year | Free of CVD, non-institutionalized, no need for a proxy respondent and expected to remain in the area for the next 3 years. | Sampled from Medicare /health care financing administration claims. | Fatal or non-fatal CHD | 302 |
| Lumley et al. (2002) | North America | 1989–1999 | Prospective cohort, augmented after 2y with African Americans | Cardiovascular health study | 5231 | Mean 73, range ≥ 65 | 42% | Median 6.3 year | Free of non-CHD CVD, not institutionalized wheelchair bound, receiving hospice treatment, or radiation therapy or chemotherapy for cancer. | Sample from Medicare /health care financing administration claims. | Fatal or non-fatal non-CHD CVD | 399 |
| Noto et al. (2002) | Europe | 1989–2000 | Prospective cohort | No name | 466 | Eligible if ≥ 60 | 48% | Study duration 11 year | Free of CVD (not reported, information achieved from contact with the authors) | All residents of a village in Sicily were invited | Fatal CVD | 59 |
| Jamrozik et al. (2000) | Australia | 1990–1994 | Cohort of controls from case-control study | Perth community stroke study | 658 | Median 75; eligible if ≥ 18 | Not reported | Study duration 4 year | Free of CVD | Selected from electoral rolls | Fatal or non-fatal CVD | 83 |
| Ahto et al. (2007) | Europe | 1990–2002 | Prospective cohort | No name | 660 | Mean 71; range 64–90 | 43% | Study duration 12 year | Free of CHD | All residents of Lieto (Finland) born in or before 1926 were invited | Fatal CVD | 60 |
| de Ruijter et al. (2009) | Europe | 1997–2004 | Prospective cohort | Leiden 85-plus study | 302 | Mean 85, range 85–85 | 29% | Study duration 5 year | Free of CVD | All residents of Leiden (the Netherlands) aged 85 were invited | Fatal CVD | 35 |
| Rodondi et al. (2012) | North America | 1997–2007 | Prospective cohort | ABC health | 2193 | Mean 74; range 70–79 | 45% | Median 8.3 year | Free of CVD, able to walk 0.25 mile and 10 stairs, and independent | Sample of whites, and all blacks in Medicare in zip code areas. | Fatal or non-fatal CHD | 351 |
| Beer et al. (2011) | Australia | 2001–2009 | Prospective cohort | HIMS | 3382 | Mean 75 (SD 4.2) | 100% | Median 6 year (IQR 5.2–7.2) | Men free of CVD | Random selection from electoral rolls | Fatal or non-fatal CVD | 686 |
| (Muscari et al., 2013) | Europe | 2003–2011 | Prospective cohort | No name | 884 | Mean 72.3 (SD 5.6) range 65–93 | 45% | Mean 6.7 year | Free of CVD | All inhabitants of a municipality in northern Italy | Fatal CVD | 28 |
| van Bussel et al. (2019a) | Europe | 2006–2015 | Prospective cohort (from neutral RCT) | preDIVA | 1811 | Mean 74 (SD 2.4) | 40% | Median 6.2 year (IQR 3.9–7.1) | Free of CVD, dementia and conditions likely to hinder successful follow-up | Random sample from GP practices | Fatal or non-fatal CVD | 277 |

Table 2
Tabular presentation for PROBAST results.

| Study | ROB | | | | Applicability | | | Overall | |
|---------------------------|--------------|------------|---------|----------|---------------|------------|---------|---------|---------------|
| | Participants | Predictors | Outcome | Analysis | Participants | Predictors | Outcome | ROB | Applicability |
| Cooney et al. (2016) | + | + | + | +/- | - | + | + | +/- | - |
| Simons et al. (2003) | + | + | + | +/- | + | + | + | +/- | + |
| Psaty et al. (1999) | + | + | + | +/- | + | + | + | +/- | + |
| Lumley et al. (2002) | + | + | + | +/- | - | + | + | +/- | + |
| Noto et al. (2002) | + | + | + | - | + | + | + | - | + |
| Jamrozik et al. (2000) | + | + | + | - | + | + | + | - | + |
| Ahto et al. (2007) | + | + | + | - | - | + | + | - | + |
| de Ruijter et al. (2009) | + | + | + | - | + | + | + | - | + |
| Rodondi et al. (2012) | + | + | + | +/- | + | + | + | +/- | + |
| Beer et al. (2011) | + | + | + | - | + | + | + | - | + |
| Muscari et al. (2013) | + | + | - | - | + | + | - | - | - |
| van Bussel et al. (2019a) | + | + | + | + | + | + | + | + | + |

PROBAST = Prediction model Risk Of Bias Assessment Tool; ROB = risk of bias.

+ Indicates low ROB/low concern regarding applicability; - indicates high ROB/high concern regarding applicability; and +/- indicates moderate ROB/moderate concern regarding applicability.

3.3. Traditional risk factors

TRF definitions varied between studies. An overview of how risk factors were defined and handled in studies is given in Table S3. Age was evaluated as continuous ($n = 8$), dichotomized ($n = 2$), or categorized ($n = 1$) predictor. Race as black vs other ($n = 2$); BMI continuous ($n = 2$), categorized ($n = 1$), or dichotomized ($n = 2$); SBP continuous ($n = 8$) or categorized ($n = 1$); DBP continuous ($n = 4$) or dichotomized ($n = 1$); hypertension dichotomized based on SBP, DBP, AHM use and/or self-report ($n = 6$); and AHM use dichotomized ($n = 6$). Diabetes was dichotomous, defined based on fasting plasma glucose levels, self-report and/or taking anti-diabetic drugs ($n = 11$). Smoking was categorized as current/former vs never ($n = 3$), current vs former/never ($n = 5$), or current, former, never separately ($n = 4$). TC, HDL and LDL were evaluated continuously ($n = 7$; 8; 3 respectively), dichotomized ($n = 2$; 1; 1) or categorized ($n = 1$; 1; 1). One study defined hypercholesterolemia based on TC (≥ 5.1 mmol/L) or lipid lowering treatment (Muscari et al., 2013). This variable was included in our analyses as TC. LVH was dichotomized ($n = 3$).

Table 3 gives an overview of TRFs from studies, with standardized effect sizes for TRFs that were retained. Fig. 2 gives the number and percentage of retained and disregarded TRFs.

Age, DM and sex were retained in most studies. SBP was retained in half. Smoking, HDL, TC, LVH, DBP and AHM were selected in a minority of the studies in which they were tested. Race, LDL, hypertension and BMI were never retained. When combined, blood pressure related variables were retained in 50%, and cholesterol related variables in 30% of studies in which they were tested. The retention of smoking was not clearly influenced by the categorization used (Table S4).

Fig. S1 presents the pooled effect sizes for each risk factor. Note that these were only reported by studies that retained them in the final model.

For some cohorts, multiple models relevant to our research question were reported. One model per cohort was chosen in counting frequencies of risk factors tested and retained, and to use in the meta-analyses, to prevent too much weight from one cohort. Ahto et al., Cooney et al., Lumley et al., and Noto et al. reported models for men and women. A risk factor was counted as retained if it was retained in one or both genders, and both were included in the meta-analyses. Simons et al. presented two models with different follow-up durations, the one with the longest follow-up (10 years) was used. When models for CHD and non-CHD CVD were reported, results were pooled into CVD (Cooney et al., 2016; Lumley et al., 2002; Psaty et al., 1999). Rodondi et al. reported three models for different methods of variable selection, the method most frequently used in other studies (backward selection based on p -value) was used in this review, to increase comparability.

3.4. Additional risk factors

All but one study, tested the incremental predictive ability of additional factors (Cooney et al., 2016). In total 55 additional variables were tested, with little overlap among studies. Twelve of these were tested in two or more cohorts (Fig. S3). Triglycerides were disregarded in all four studies, and C-reactive protein in 75% (3 of 4 studies). 'Number of drugs' and homocysteine were evaluated in 2 studies, and retained in both (100%).

3.5. Performance

Discriminatory performance of models with TRFs only, and models with relevant TRFs enhanced with additional risk factors, was reported in six studies (Table S5). C-statistics ranged from 0.53 (95% CI 0.42–0.63) to 0.74 (95% CI not reported) for TRF-only models, and from 0.61 (95% CI not reported) to 0.77 (95% CI not reported) for enhanced models. C-statistics of the enhanced models were generally slightly higher than those of the TRF-only models. Number of included variables for the TRF-only models ranged from 6 to 9, and from 1 to 12 for the enhanced models (Table S5). Only four out of 12 studies reported calibration measures.

3.6. Subgroup and sensitivity analyses

Subgroup results were consistent with the main analyses, with age, sex, and DM having the highest retention rates (Fig. S2). Compared to studies with fatal CVD as outcome (5 studies), in studies with combined fatal and non-fatal CVD (6 studies) the risk factors DM, sex, SBP and smoking were more often retained. Subgroup analysis in studies with a moderate to low risk of bias, (6 studies representing 5 cohorts) yielded similar results, although retaining rates for SBP, smoking, and HDL were somewhat higher (60–80%) than for all studies combined ($\leq 50\%$). In the subgroup of studies that included participants without a history of CVD at baseline (9 studies), results were essentially the same as for the main analyses. The subgroups for CHD, non-CHD CVD, men, and women were too small to interpret.

4. Discussion

In this systematic review, based on 12 studies from 11 unique cohorts, the main predictors for first incident CVD in people aged 60+ were age, sex and diabetes in the majority of cohorts. Based on studies with moderate to low risk of bias including SBP, HDL cholesterol and smoking seem to have predictive value. Other blood pressure and

Table 3
Overview of traditional risk factors tested, retained and disregarded with effect sizes.

| Study | Outcome, group | Effect measure | Age (per 1 year increment) | Sex (female) | Race (black) | SBP (per 10 mmHg) | DBP (>70 vs <70 mm Hg) | Hypertension | AHM use | Diabetes mellitus | Smoking (smoker vs non-smoker ¹) | TC per 1 mmol/L | HDL per 1 mmol/L | LDL | BMI | LVH |
|-----------------------------|---------------------------|----------------|----------------------------|----------------------|--------------|-------------------|------------------------|--------------|------------------|-------------------|--|------------------|------------------|-----|-----|------|
| Cooney (2016) | Fatal CVD, men (pooled) | HR | 1.14 (1.13–1.15) | STR | NT | 1.08 (1.05–1.10) | NT | NT | NT | 1.74 (1.51–1.99) | 1.78 (1.62–1.95) | 1.23 (1.17–1.30) | 0.84 (0.80–0.89) | NR | NR | NT |
| | Fatal CVD, women (pooled) | HR | 1.17 (1.16–1.18) | STR | NT | 1.08 (1.06–1.09) | NT | NT | NT | 2.09 (1.83–2.39) | 1.69 (1.49–1.92) | 1.13 (1.07–1.19) | 0.84 (0.80–0.89) | NR | NR | NT |
| Simons (2003) | CVD | OR | 1.08 (1.06–1.09) | 0.55 (0.43–0.71) | NT | 1.10 (1.05–1.16) | NT | NT | 1.46 (1.16–1.85) | 1.69 (1.14–2.53) | 1.41 (1.04–1.91) | 1.20 (1.10–1.32) | 0.77 (0.56–1.08) | NR | NR | NT |
| Psaty (1999)/Lu mley (2002) | CVD | HR | 1.04 (1.01–1.07) (F) | 0.38 (0.28–0.52) (F) | NR | 1.13 (1.06–1.20) | NR | NR | NR | 1.68 | NR | NR | NR | NR | NT | 1.65 |
| Noto (2002) | Fatal CVD, men | OR | 3.1 (1.7–5.7) | STR | NT | NT | NT | NR | NT | NR | NR | NR | NR | NR | NR | NR |
| | Fatal CVD, women | OR | 3.0 (1.5–6.0) | STR | NT | NT | NT | NR | NT | 3.0 (1.0–9.3) | NR | NR | NR | NR | NR | NR |
| Jamrozik (2000) | CVD | HR | 1.23 (0.89–1.68) (F) | 0.76 (0.48–1.21) (F) | NT | NT | NT | NT | NT | 2.14 (1.06–4.32) | NR | NT | NT | NT | NT | NT |
| Ahto (2007) | Fatal CVD, men | HR | 1.09 (1.04–1.14) * | STR | NT | NT | NT | NR | NT | NR | NR | NT | NT | NT | NR | NT |
| | Fatal CVD, women | HR | 1.08 (0.99–1.17) (F) * | STR | NT | NT | NT | NR | NT | NR | NR | NT | NT | NT | NR | NT |
| de Ruijter (2009) | Fatal CVD | HR | NT | NR | NT | NR | NT | NT | NT | NR | NR | NR | NR | NT | NT | NR |
| Rodondi (2012) | CHD | HR | 1.03 (0.99–1.07) (F) | 0.62 (0.45–0.86) | NR | 1.09 (1.02–1.16) | NR | NR | NR | 1.46 (1.10–1.95) | 1.31 (0.99–1.74) | NR | 0.98 (0.96–1.00) | NR | NT | NT |
| Beer (2011) | CVD, men | HR | 2.00 (1.70–2.34) * | NT | NT | NR | 1.46 (1.20–1.77) | NR | NT | NR | NR | NR | NR | NR | NR | NT |
| Muscari (2013) | Fatal CVD | HR | 4.67 (1.98–11.44) * | NR | NT | NR | NR | NR | NR | NR | NR | NR | NR | NT | NR | NT |
| van Bussel (2019) | CVD | HR | 1.03 (0.98–1.08) (F) | 0.70 (0.57–0.88) | NT | NR | NR | NT | NR | 1.40 (1.07–1.83) | 1.73 (1.31–2.28) | NR | NR | NR | NR | NT |

CVD, cardiovascular disease; CHD, coronary heart disease; HR, hazard ratio; OR, odds ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; AHM, antihypertensive medication; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; BMI, body mass index; LVH, left ventricular hypertrophy. STR, stratified; NR, not retained in the final model; NT, not tested. (F), forced into the model. Color coding refers to handling in count and meta-analyses. Green, retained; red, disregarded; gray, not tested.

1. Non-smoker is defined as never and past smoker.

* HR for age ≥ 75 year compared to age < 75 year.

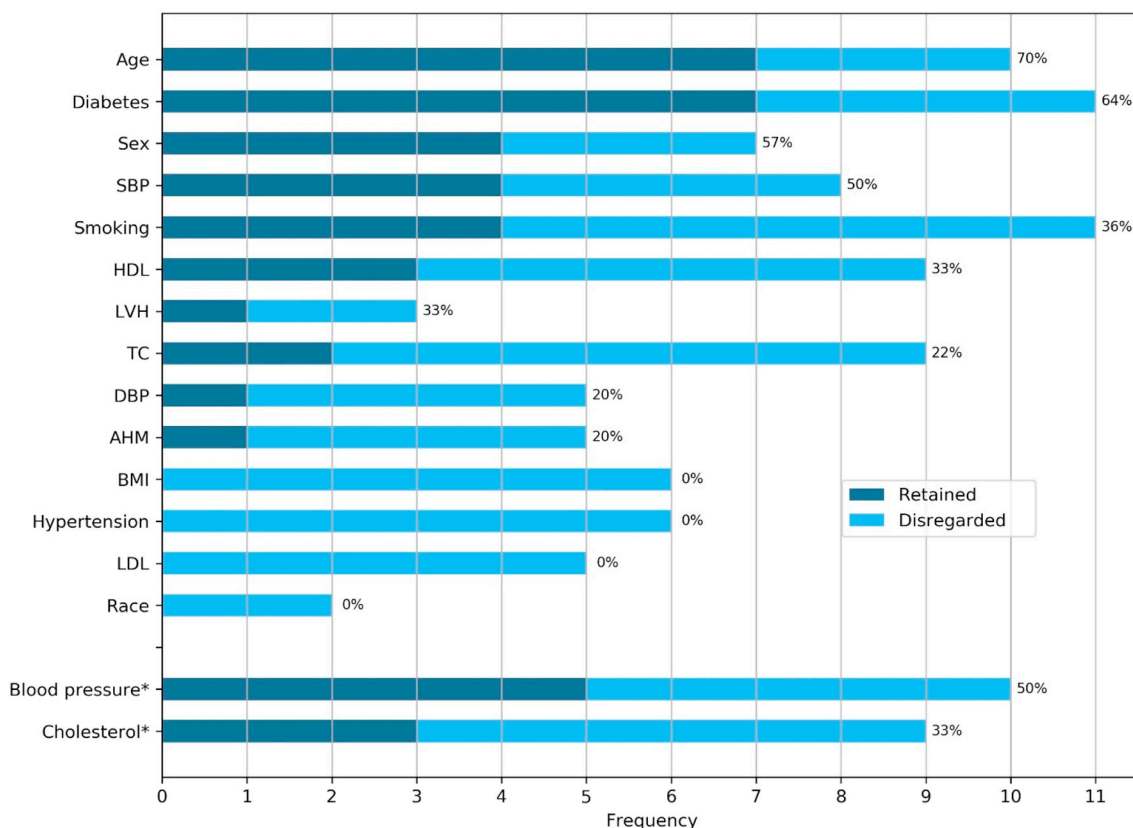


Fig. 2. Traditional risk factors – frequency retained and disregarded.

The total length of the bar represents the frequency a TRF was tested. The percentage that a TRF was retained is given at the right side of each bar.

*Blood pressure, composite of SBP, DBP, hypertension and AHM. Cholesterol, composite of TC, HDL and LDL cholesterol.

SBP, systolic blood pressure; HDL, high density lipoprotein cholesterol; LVH, left ventricular hypertrophy; TC, total cholesterol; DBP, diastolic blood pressure; AHM, antihypertensive medication use; BMI, body mass index; LDL, low density lipoprotein cholesterol.

cholesterol related variables, BMI, race and LVH seem of very limited or no additional value. Model performance was with C-statistics ranging from 0.61 to 0.77 moderate at best. Studies were heterogeneous in terms of era, number and kind of TRFs that were tested, the outcome event, follow-up duration, and risk of bias, which limited comparability of the results.

In middle aged adults CVD prediction models generally perform slightly better, median C-statistics of *validated* well-known models ranging from 0.66 to 0.79 (Damen et al., 2016). Though there is much overlap, this supports previous findings that risk factors better predict CVD in middle aged than in older persons.

4.1. Traditional risk factors

The predictive value of DM seems to attenuate with increasing age, but may remain relevant up to high age. In this review DM appeared a relevant predictor, but mostly in cohorts with a relatively low mean age (75% retained in cohorts with a mean age < 75 vs 30% in ≥ 75). Moreover, the effect size for DM in this review (HR 1.75 (95%CI 1.52–2.01)) was lower than that for middle-aged persons, e.g. in the QRISK cohort a hazard ratio of 2.95 (95%CI 2.76–3.15) was reported for persons aged 43 years (Hippisley-Cox et al., 2010). While the association of SBP with CVD has been reported to decrease or reverse with increasing age (Ahmadi et al., 2015; Hippisley-Cox et al., 2010; Lind et al., 2018), conflicting results have been reported for cholesterol (Houterman et al., 2000; Lind et al., 2018). The predictive value of cholesterol might depend on type of cholesterol, study outcome, participant age at evaluation and comorbidities (Ahmadi et al., 2015). This review suggests that SBP and HDL might be valuable for CVD

prediction, whereas other blood pressure and cholesterol related variables seem of limited value. Interpretation of the predictive value of blood pressure and cholesterol is complicated because treatment of these factors initiated after baseline could have reduced their predictive ability (Sperrin et al., 2018). Studies included in this review generally failed to report or account for treatment at baseline or during follow-up. In daily practice this is not problematic since persons with and without cardiovascular medication receive (repeated) risk assessments. However, the predictive value of hypertension and dyslipidaemia in these models is uninformative of the risk that untreated hypertension or dyslipidaemia may convey in older people and, crucially, the lack of association with adverse outcomes does not mean these conditions should not be treated or that treatment can safely be discontinued (Pajouheshnia et al., 2017; Sperrin et al., 2018). In this review BMI had no predictive value. However, the relation between BMI and CVD may follow a U-shaped curve, inadvertently leading to the conclusion that BMI conveys no predictive value (Ahmadi et al., 2015; Lind et al., 2018). Previous studies found a higher risk of CVD among African-Americans compared to others, which was fully attributable to the burden of cardiovascular risk factors among African-Americans (Feinstein et al., 2012; Safford et al., 2012). This is in line with the lack of predictive ability for race in this review. However, this does not exclude that other definitions of race/ethnicity may yield more appropriate predictors for CVD, either through genetic or environmental factors (Agyemang et al., 2005). Though not demonstrated through exploration of different operationalisations (Table S4), specific definitions of smoking may have masked any predictive value of smoking in this review. Ideally, future research should use ‘ex-smoker’ as a separate category and take into account time since cessation (Mons et al., 2015).

Associations of TRFs with CVD may be different for CHD and non-CHD CVD. In a study with 32 years of follow-up, the relation of SBP with stroke was stronger than with myocardial infarction, in all age categories between 50 and 77 (Lind et al., 2018). Differences in predictive value between CHD and non-CHD CVD outcomes could not be studied in this review, due to insufficient information. Although the greater predictive value of risk factors in the combined fatal/non-fatal CVD subgroup may reflect a higher number of events and more statistical power, risk factors may truly have higher predictive value for the combined outcome event compared to fatal CVD only.

4.2. Why associations shift in older people

Age itself may merely reflect exposure time to the other risk factors. Atherosclerosis and thrombosis cause vascular damage throughout life, possibly decreasing relative contributions of the TRFs with increasing age (Vliegthart et al., 2005). Because all included studies report relative risk rather than absolute risk differences, diminished associations may partly be explained by the a-priori risks of CVD which also increase with aging. Although statistical power increases with higher baseline risk, the potential for a large relative risk decreases (Text S2, Table S6) (Hochman and McCormick, 2011). Furthermore, part of the population that is sensitive to the TRFs may already have developed CVD, leaving the CVD free population with inherent inherently lower susceptibility to cardiovascular risk factors, in which associations are diminishing or even reversed (Kannel and Vasani, 2009). Finally, older persons form a heterogeneous group regarding multi-morbidity, life-expectancy, and frailty, diluting predictive value of TRFs and complicating generalizability (Ahmadi et al., 2015; Jansen et al., 2015).

4.3. Additional CVD predictors in old age

Potential non-traditional CVD predictors in older people have been widely explored. Of these, homocysteine, coronary calcium score and frailty seem promising predictors (de Ruijter et al., 2009; Vaes et al., 2017; Veronese et al., 2017; Vliegthart et al., 2005). Including the coronary calcium score demonstrated improved accuracy of currently applied risk scores for predicting CVD outcomes (Yeboah et al., 2012). Moreover, both the coronary calcium score and homocysteine levels may help to identify patients likely to benefit from statin therapy (Drewes et al., 2014; Mitchell et al., 2018). Previous meta-analysis identified frailty and pre-frailty as significant predictors for CVD, and interestingly, in frail persons the association between TRFs and mortality diminished (Vaes et al., 2017; Veronese et al., 2017). From the potential non-traditional risk factors evaluated in included studies, homocysteine and 'number of drugs' seemed most propitious, being retained in both studies in which they were tested. However, numbers were too low to draw conclusions.

4.4. Methodological considerations of included articles

The quality of studies included in this review varied. The most frequent sources of bias generally cause overestimated effect sizes, or increased uncertainty of the outcomes. Lower quality scores are partly explained by setting high statistical standards, including more recent developments such as multiple imputation and accounting for competing risks, which were not widely adopted at the time of those studies (Koller et al., 2012b; Selmer et al., 2017). Since in older people non-cardiovascular mortality increasingly precludes CVD events, not considering competing risks may cause overestimation of CVD risk and effect sizes (Koller et al., 2012a; Selmer et al., 2017).

4.5. Strength and limitations of this study

A strength of this systematic review is the focus on predictors specifically identified in older people, since literature and clinical

knowledge are biased by a history of extrapolating risk factors in middle aged persons to older persons.

A limitation is that included studies evaluated different sets of traditional and non-traditional risk factors, which influences the predictive value of individual risk factors in multivariable models, and their chance of being retained. For example, homocysteine was tested in two studies, and in those studies, zero and two TRFs were retained in the model (Beer et al., 2011; de Ruijter et al., 2009). Theoretically, homocysteine is such a strong predictor that it offsets the predictive value of other risk factors and inclusion of homocysteine into all other studies could have led to disregarding more TRFs in those models.

The meta-analyses presented in this review should be interpreted with some caution. They represent the selection of effect sizes for TRFs that were retained during the variable selection process – and thus may overestimate the true association (Heinze et al., 2018). Substantial heterogeneity exists between models of which risk factor estimates were pooled (Riley et al., 2019). Further, different types of prognostic effect measures (HR and OR) were pooled, some estimates lacked standard errors and could not be pooled, estimates relate to various follow-up durations, and different methods of measurements and variable definition and approaches to handling continuous prognostic variables were applied. In conclusion, pooled effect sizes of TRFs are likely overestimations, and may best be interpreted as an optimistic estimate of the effect size for the TRFs, in the older population.

4.6. Implications for clinical practice and further research

Since model performance of most models is moderate at best, current CVD prediction models for older people can assist clinical practice by broadly classifying patients into risk categories. For subsequent treatment decisions patient preferences and concerns should be taken into account (van Bussel et al., 2019a). To improve model performance, relevant TRFs found in this review should be supplemented with yet to be evaluated, relevant non-traditional risk factors. Further, adequate statistical methods such as accounting for competing risks of death and inflated confidence, should be employed to prevent overestimation of risks. Such a model should be derived and validated in a large cohort of community dwelling older persons.

Alternatives to common prediction practices may be considered to improve risk communication. Predicting short term relative risk (i.e. 5-year instead of 10-year risk), heart age, or absolute risk difference after initiation of treatment might be preferable in older populations (Hill et al., 2010; Jackson, 2014; van der Leeuw et al., 2014; Tabaei et al., 2019; Wells et al., 2010).

With the widespread implementation of treatment of hypertension, dyslipidaemia, and other risk factors throughout health care, little is known about the natural course and associations of these conditions in old age. Since obtaining such information in a randomized setting by withholding treatment is ethically and practically challenging, comprehensive observational cohort studies with sufficient information and detail to account for the myriad of possible biases may still offer important opportunities to explore these relations, despite the limitations to infer true causal pathways from such studies.

5. Conclusion

This review recommends CVD risk prediction in people aged 60+ to be based on age, sex and diabetes, and to further evaluate the incremental predictive value of SBP, HDL cholesterol, smoking and non-traditional risk factors such as homocysteine, frailty and coronary calcium score. Other blood pressure and cholesterol related variables, BMI, and LVH hardly seem of any additional predictive value and can be disregarded in CVD prediction in older people.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ypmed.2020.105986>.

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