



## Who exceeds ATP-III risk thresholds? Systematic examination of the effect of varying age and risk factor levels in the ATP-III risk assessment tool<sup>☆</sup>

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### ABSTRACT

**Objective.** We sought to determine the levels of risk factors required to exceed threshold values of intermediate ( $\geq 10\%$ ) or high ( $>20\%$ ) predicted 10-year risk for coronary heart disease using the Adult Treatment Panel III (ATP-III) Risk Assessment Tool.

**Methods.** Continuous risk factor values were entered into the risk assessment tool to examine levels of predicted 10-year risk. Both individual risk factors and the joint effects of varying multiple risk factors were systematically examined.

**Results.** Women only exceed 10% risk at ages  $\geq 70$  with single risk factors of HDL-cholesterol levels  $<30$  mg/dL or systolic blood pressure  $>170$  mm Hg. Women  $\leq 65$  only exceed 10% risk if they are smokers with low HDL-cholesterol levels. In contrast, single risk factors can cause men over 45 to exceed 10% or 20% predicted 10-year risk. Combinations of only modestly elevated risk factors cause many men to exceed 10% risk at ages  $\geq 45$ , and to exceed 20% risk at ages  $\geq 55$ .

**Conclusions.** Because such high-risk factor levels are required for men  $<45$  years and women  $<65$  years to exceed ATP-III risk thresholds, additional means for risk communication may be needed for individuals with elevated risk factors in these age ranges.

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### Introduction

The major assumption underlying current prevention guidelines is that the intensity of preventive treatment should match the level of absolute risk (Expert Panel, 2002). Accordingly, the National Cholesterol Education Program's Third Adult Treatment Panel (ATP-III) developed a multivariable risk assessment tool (National Cholesterol Education Program, 2002) to estimate absolute 10-year risk for fatal and non-fatal myocardial infarction using seven traditional risk factors: sex, age, total cholesterol, HDL-cholesterol, systolic blood pressure, smoking status, and current treatment for hypertension. The tool is accessible to any health care provider or patient through the National Heart, Lung, and Blood Institute website (National Cholesterol Education Program, 2002).

This risk estimate can be used by clinicians to communicate risk and determine the need for medical therapy. In the ATP-III algorithm, individuals with diabetes or estimated 10-year risk  $>20\%$  are considered to be at high risk, and they are recommended for immediate drug therapy to lower risk (Expert Panel, 2002). Those

with a predicted 10-year risk of 10% to 20% are considered to be at intermediate risk. Within this stratum, clinicians and patients have the option to begin drug therapy, or they may pursue additional noninvasive testing to further stratify risk and assist in decision-making regarding drug therapy. Finally, those with estimated 10-year risk  $<10\%$  are considered by the algorithm to be "low" risk. Newer guidelines (Grundy et al., 2004) recommend the incorporation of risk factor counting to guide risk classification and LDL-cholesterol (LDL-c) treatment goals in these individuals. Patients with  $<10\%$  10-year risk and 0–1 traditional risk factors are considered "lower risk" and have a LDL-c goal of  $<160$  mg/dL, and those with 2 or more risk factors are considered "moderate" risk with a LDL-c goal of  $<130$  mg/dL.

Prior studies have examined the prevalence of different risk strata (i.e., proportion of the population with 10-year predicted risk  $<5\%$ , 5% to  $<10\%$ , 10% to 20%,  $\geq 20\%$ ) (Ford et al., 2004; Keevil et al., 2007; Persell et al., 2006), while others have examined the predictive performance of the ATP-III risk assessment tool in different populations (D'Agostino et al., 2001; Daviglius et al., 2004) and in younger individuals (Berry et al., 2007). It appears relatively easy for clinicians to identify very low risk and very high-risk individuals based simply on the absence of risk factors or the presence of multiple elevated risk factors (Grover et al., 1995). However, because covariates are weighted in risk prediction equations, risk estimates may not be intuitive (Ridker and Cook, 2005) for the majority of patients. Thus, a more thorough understanding of the intrinsic properties of the ATP-III

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risk assessment tool itself would be useful to clinicians. The objective of the present study was to perform a systematic evaluation of the ATP-III online risk assessment tool to determine: what levels of risk factor burden are required to exceed treatment thresholds of  $\geq 10\%$  or  $>20\%$ , and which age, sex and risk factor combinations are classified by the tool as “low” risk even in the face of high-risk factor burden.

**Methods**

The online risk assessment tool from ATP-III incorporates age, sex, total and HDL-cholesterol levels, smoking status, systolic blood pressure, and treatment for hypertension into a multivariable regression equation to estimate the 10-year risk for hard CHD (coronary death or non-fatal myocardial infarction). We entered data into the ATP-III online risk assessment tool for men and women using 5 year intervals from ages 30 (the minimum age allowed) to 75 years. Our approach did not use specific individuals or a specific population; instead, it allowed us to examine the effects of varying individual risk factors and aggregate risk factor burden on predicted 10-year risks for coronary events using the ATP-III online risk assessment tool. This tool is based on equations derived from the Framingham cohorts (Expert Panel, 2002).

*Risk calculation procedure for single risk factors*

To compare the effect of individual risk factor levels on 10-year predicted risk, we varied single risk factor levels, holding the other

risk factor levels constant at approximate age-adjusted national means (systolic blood pressure: 130mm Hg; total cholesterol: 200 mg/dL; HDL-cholesterol: 45 mg/dl for men and 55 mg/dl for women) (Gregg et al., 2005). Using the entire range of values permitted by the risk assessment tool, we varied total cholesterol from 130 to 320 mg/dL in increments of 10 mg/dL, HDL-cholesterol from 20 to 100 mg/dL in increments of 5 mg/dL, and systolic blood pressure from 90 to 200 mm Hg in increments of 10 mm Hg. We also compared the predicted risks for smoking vs. non-smoking status and for treatment with antihypertensive therapy vs. no treatment, holding other risk factor levels constant as described above. For example, to determine the effect of untreated systolic blood pressure on 10-year risk in a 45-year old woman, we set total cholesterol equal to 200 mg/dL, HDL-cholesterol to 55 mg/dL, and smoking status and antihypertensive therapy to “no” while we varied systolic blood pressure from 90 mm Hg to 200 mm Hg.

*Risk calculation procedure for multiple risk factors*

To examine the effect of risk factor combinations on 10-year risk estimates, we varied the levels of all risk factors in every possible combination for all ages. After consideration of average and at-risk values of risk factors, we present representative risk factor levels as follows. For total cholesterol, we included values of 160 mg/dL, 200 mg/dL, and 240 mg/dL. For systolic blood pressure, we included 110 mm/Hg, 130 mm Hg, and 150 mm Hg. For HDL-cholesterol in men, we included 25 mg/dL, 35 mg/dL, and 45 mg/dL. For HDL-cholesterol

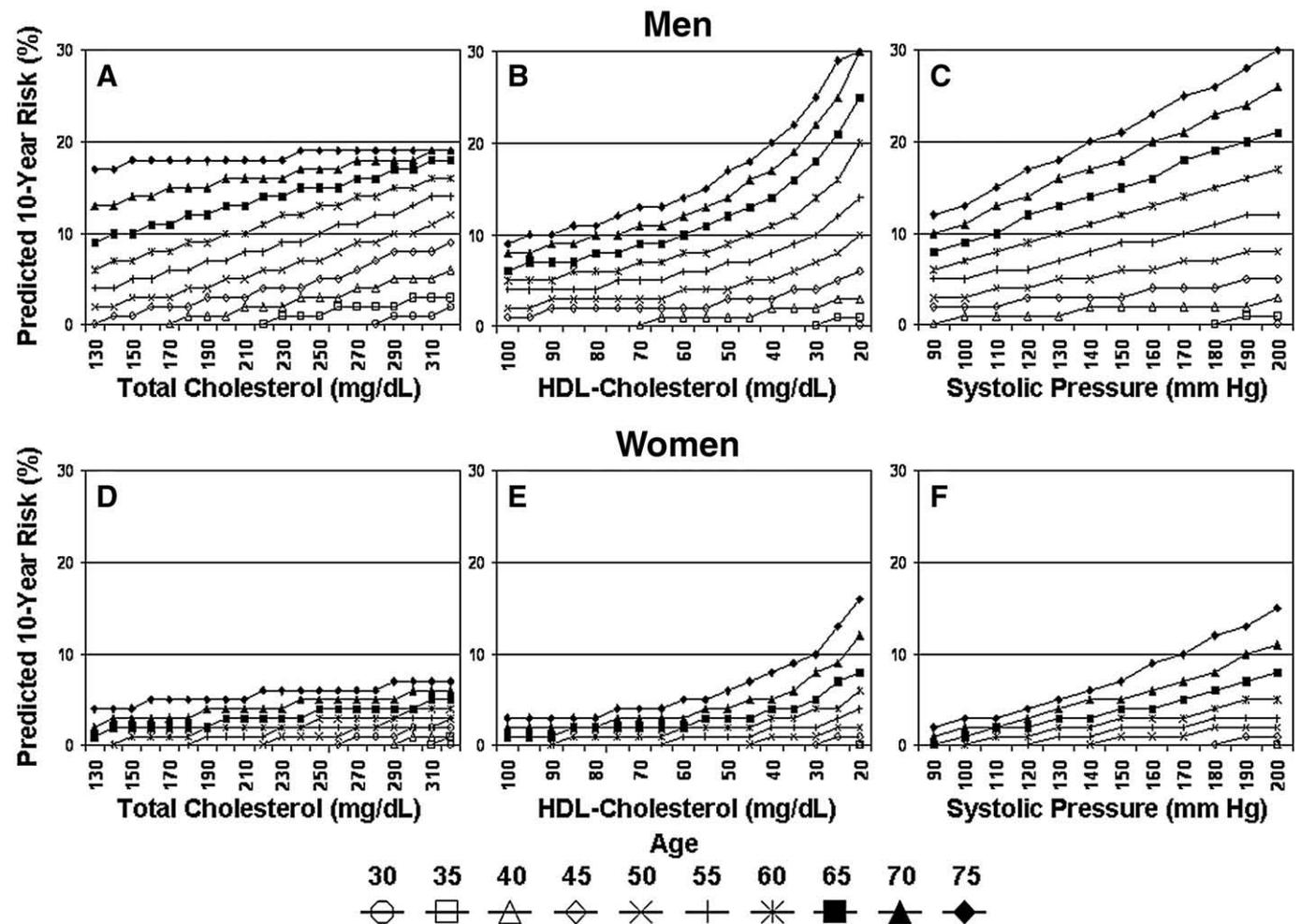


Fig. 1. Ten-year predicted risks, using the ATP-III Risk Assessment Tool, across levels of single risk factors in men (Panels A–C) and women (Panels E–F) at selected ages, with other risk factors held constant at approximate age-adjusted average values.

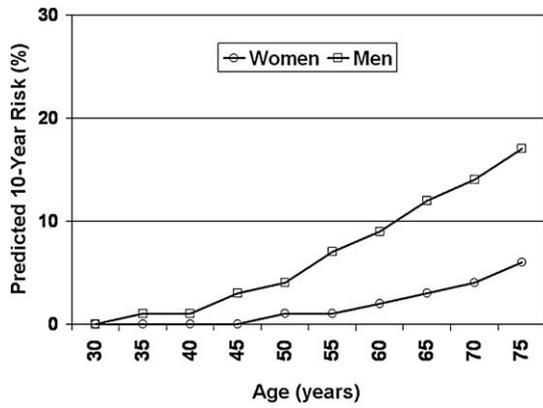


Fig. 2. Ten-year predicted risks, using the ATP-III Risk Assessment Tool, for men and women at selected ages, with risk factors held constant at approximate age-adjusted average values.

in women, we included 35 mg/dL, 45 mg/dL, and 55 mg/dL. In this set of analyses, we varied smoking status for all risk factor combinations. In secondary analyses, we varied antihypertensive therapy as well. This procedure was repeated for all ages in men and women.

**Results**

*Single risk factor effects*

Holding all other risk factors constant, we observed different patterns of effects for variation in single risk factors on 10-year predicted risk. For HDL-cholesterol in men, the risk assessment tool produces a curvilinear distribution of 10-year risk with a marked increase in predicted risk at HDL-cholesterol levels below 60 mg/dL.

When average HDL-cholesterol levels are selected, data from the risk assessment tool indicate that men  $\geq 60$  years old have a 10-year risk estimate of  $> 10\%$  (Fig. 1). For systolic blood pressure, the tool produces a more linear risk estimate across all levels of blood pressure for men at the same age. In contrast, the effects of varying total cholesterol are more modest, particularly for men of older ages. For example, the predicted 10-year risk remains near the 20% threshold for all levels of total cholesterol in men age 75 years in contrast to the marked variation in 10-year risk across levels of HDL-cholesterol and systolic blood pressure (Fig. 1). Finally, the presence of smoking alone with average risk factor values in men  $\geq 45$  years produces a 10-year predicted risk of  $> 10\%$  in most circumstances (data not shown).

As expected, the 10-year predicted risk was much lower in women compared to men across all ages (Fig. 2). Whereas women do not cross the 10% threshold at any age with average risk factor levels, all men over age 60 achieve a  $> 10\%$  predicted risk when average risk factor levels are entered into the risk assessment tool. This dichotomy in risk between women and men is seen across all levels of single risk factors (Fig. 1), including total cholesterol, HDL-cholesterol, and systolic blood pressure. In fact, a 10-year risk estimate  $> 10\%$  was observed only for women aged  $\geq 70$  years when the extremes of HDL-cholesterol or systolic blood pressure were entered (Fig. 1).

*Effect of risk factor combinations*

In men, combinations of only modestly elevated risk factors with smoking allow men age 45 years (Fig. 3) to exceed 10% and men age 55 years to exceed 20% predicted 10-year risk. By age 65, virtually all men exceed 10% predicted 10-year risk, even with risk factor levels selected in the desirable range. In contrast, most women at age 55 (and younger) do not exceed the 10% threshold regardless of risk factor burden. Only the combination of smoking with marked abnormalities in HDL-cholesterol, total cholesterol, and systolic blood pressure

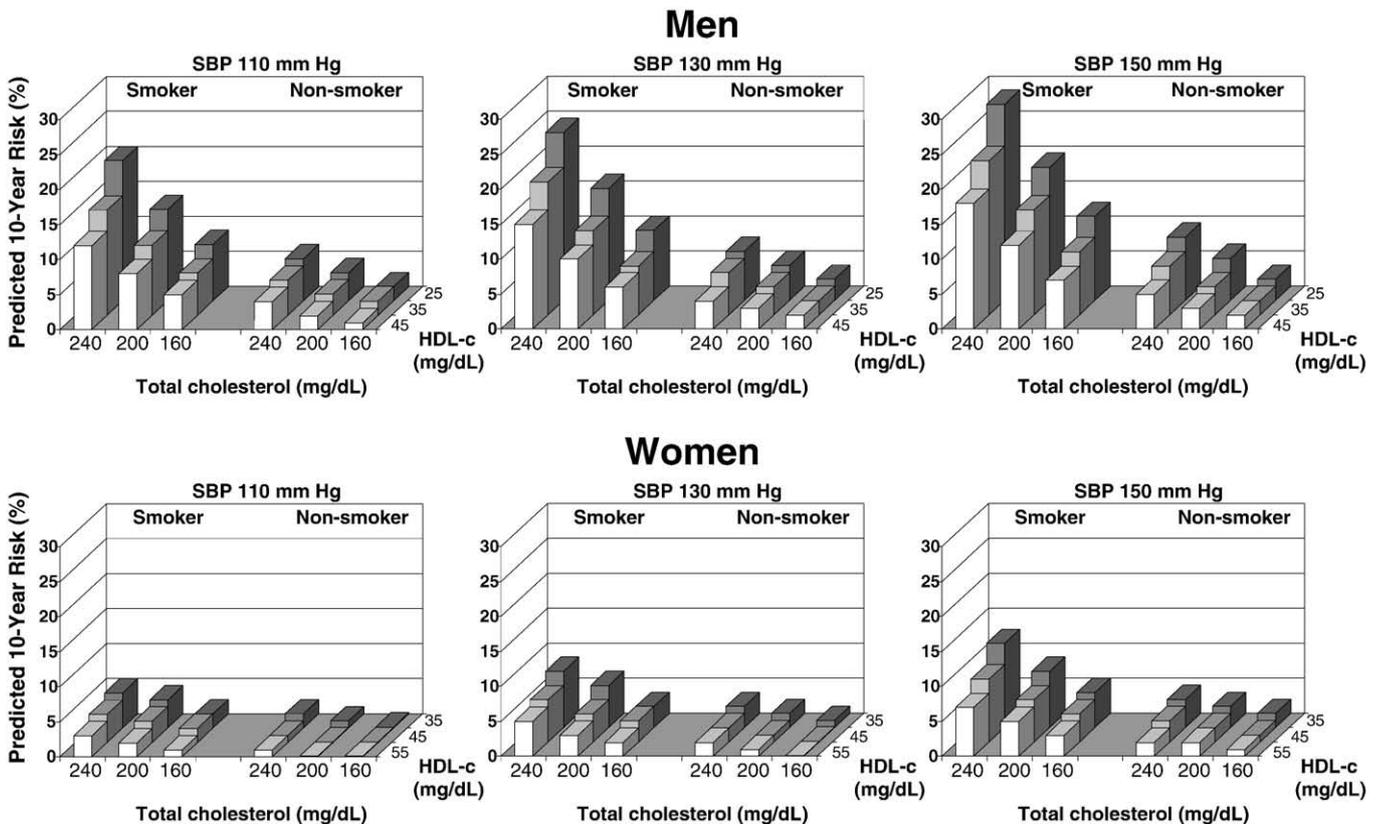


Fig. 3. Ten-year predicted risks, using the ATP-III Risk Assessment Tool, across levels of multiple risk factors in men at age 45 years and women at age 65 years.

produces a 10-year predicted risk of >10% for women at ages  $\geq 65$  (Fig. 3). However, by age 75, smoking and only modest elevation in risk factors result in a 10-year predicted risk of >10% in most women. For most combinations of risk factors, even with extreme values, non-smoking men <45 years of age and women <65 years of age have 10-year predicted risks <10% (Fig. 3).

## Discussion

In this systematic examination of the properties of the online ATP-III risk assessment tool, we had several important findings. First, the tool estimates 10-year risk for hard CHD to be <10% across a large spectrum of ages and risk factor levels, including non-smoking men <45 years and virtually all women <65 years old. Second, some risk factor profiles nearly always yield an “intermediate” or “high” 10-year risk estimate. For example, men who smoke and/or who are >65 years generally have a predicted 10-year risk  $\geq 10\%$ , regardless of other risk factor burden. Finally, we found that the ATP-III tool produces some interesting patterns in the effect of isolated adverse risk factors (particularly HDL-cholesterol) on 10-year predicted risk.

Prior studies have indicated that extension of the FRS to younger age ranges has some limitations. Recently, we found that the FRS classified *all* men <30 years as “low risk” by ATP-III definitions, despite substantial risk factor burden (Berry et al., 2007). These findings parallel other studies of the prevalence of 10-year risk estimates in the population. For example, using nationally representative data on risk factor levels, one study found that most men <50 years and most women <70 years have a 10-year risk estimate of <10% (Ford et al., 2004). More recently, others have shown the unique contributions of both “risk factor counting” and 10-year risk estimates to risk classification (Keevil et al., 2007; Persell et al., 2006). Similar to our findings, a prior analysis of data from the NHANES and Framingham Heart Study found that elevated risk factors rather than borderline risk factors accounted for the majority of CHD risk in the population (Vasan et al., 2005). In the present study, we extended these prior observations to an analysis of the intrinsic properties of the risk assessment tool itself.

### Clinical implications

Over the past two decades, the development of global risk estimation tools has allowed the incorporation of established risk factors into multivariable models to predict the absolute risk for CHD or CVD over a 10-year period. These global risk scores aid primary prevention efforts by helping to identify high-risk patients who may benefit most from drug therapy in the near-term (Expert Panel, 2002; Wilson et al., 1998). Ten-year risk estimates may also aid in communication of risk to promote therapeutic lifestyle changes, promote adherence to therapy, and/or modify treatment goals (Grundey et al., 1999).

The ATP-III algorithm applies clinical thresholds to the risk estimates provided by the ATP-III risk assessment tool. As such, the risk assessment tool classifies virtually all women and most non-smoking men aged <45 years as low risk, even in the face of significant risk factor burden. These results suggest that additional means for risk estimation and communication, in conjunction with the current model, may be needed to help younger individuals understand the importance of addressing multiple moderate or single elevated risk factors for long-term CHD prevention.

### Alternative approaches to risk estimation

Several possible alternative strategies have been proposed for risk estimation and communication in younger patients (Berry et al., 2007). Using the current treatment thresholds recommended by ATP-III, clinicians could postpone treatment until 10-year predicted

absolute risk exceeds 10% or 20%. This approach, however, dismisses the clinical importance of risk factor burden and the fact that long-term exposure to elevated risk factors is a critical determinant of later disease. As Sniderman and Furberg (2008) recently observed, by estimating risk over the short term (i.e., the next 10 years) with age as an independent risk factor in the equations, major guidelines discourage drug treatment until clinical events are common, in older age. Therefore, this strategy has no effect on lowering short-term risk in younger patients, and sub-optimal effects on long-term risk, since treatment introduced at some older age cannot fully compensate for the earlier decades with high-risk factor levels. Others have suggested use of *relative* risk estimation for younger patients with low short-term absolute risk (Ridker and Cook, 2005). Although this approach may overcome the significant weighting of age in the risk equations, it is often difficult for patients and clinicians to understand the meaning of relative risks, especially when baseline risk is low (Edwards et al., 2002; Vasan and D'Agostino, 2005).

Creating lower thresholds for classifying risk in younger individuals (e.g. >5% instead of 10% for intermediate risk) represents a third potential strategy for risk classification and communication. However, short-term risk estimates in younger individuals often do not discriminate remaining lifetime risk well (Lloyd-Jones et al., 2004). For example, when men at age 40 were stratified by their 10-year Framingham risk scores, 10-year event rates differed markedly, as expected, whereas lifetime risks for CHD were nearly as high for those in the lowest tertile compared with those in the highest tertile of 10-year predicted risk, likely due to changes in risk factors and competing risks over time. Thus, this approach could potentially commit large numbers of individuals to life-long drug therapy with unknown expectation of benefit and limited safety data beyond 10 to 15 years. Finally, some have recommended routine subclinical disease imaging such as coronary calcium scoring or carotid intima-media thickness measurement for most US adults (Naghavi et al., 2006). Although potentially applicable in limited circumstances, data are lacking on the safety, prognostic significance and cost-effectiveness of routine imaging in younger individuals.

Given the limitations of the above strategies, lifetime risk estimation represents an attractive approach to enhance risk communication to younger individuals with low 10-year absolute risk but high-risk factor burden (Lloyd-Jones et al., 2006, 2003). In concert with 10-year risk estimates, lifetime risk estimates may provide a better understanding of an individual's true risk for CHD and may motivate changes in lifestyle or adherence to therapy. Because lifetime risk estimates, like 10-year risk estimates, reflect the average experience of large cohorts, caution must be exercised when applying them to individual patients. Every patient has a unique risk for developing CHD based on a combination of traditional risk factor levels and genetic predisposition. These unique aspects should be considered when negotiating a primary prevention strategy for any patient. However, long-term risk assessment may represent an important adjunctive strategy for younger patients in whom exclusive attention to short-term risks may discourage lifestyle modification or adherence to therapy.

### Study limitations

In the present study, we excluded diabetes from our 10-year risk estimate for CHD because we used the ATP-III online risk assessment tool. ATP-III considers diabetes a CHD-risk equivalent (Expert Panel, 2002), so the data we report are relevant to the practicing physician focusing on primary prevention. Similarly, LDL-c level is excluded from our analysis because it too is not a risk factor in the ATP-III online tool. While LDL-c plays an important role in the initiation of pharmacotherapy under new guidelines, total cholesterol is most often measured clinically. Finally, because the ATP-III risk assessment tool was derived in the Framingham cohort, an exclusively Caucasian

sample, this may limit the ability to generalize some of these findings to other ethnicities (D'Agostino et al., 2001).

## Conclusions

Because of the weighting of covariates in the ATP-III risk assessment tool model, 10-year risk estimates for hard CHD may not be intuitive for clinicians and patients. The present study provides a more thorough understanding of the *intrinsic properties* of the ATP-III risk assessment tool itself. Importantly, because such high-risk factor levels are required for men <45 years and women <65 years to exceed ATP-III risk thresholds, additional means for risk communication may be needed for men and women with risk factors in these age ranges.

## Conflict of interest statement

The authors declare that there are no conflicts of interest.

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