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The challenge of risk estimation in cardiovascular prevention

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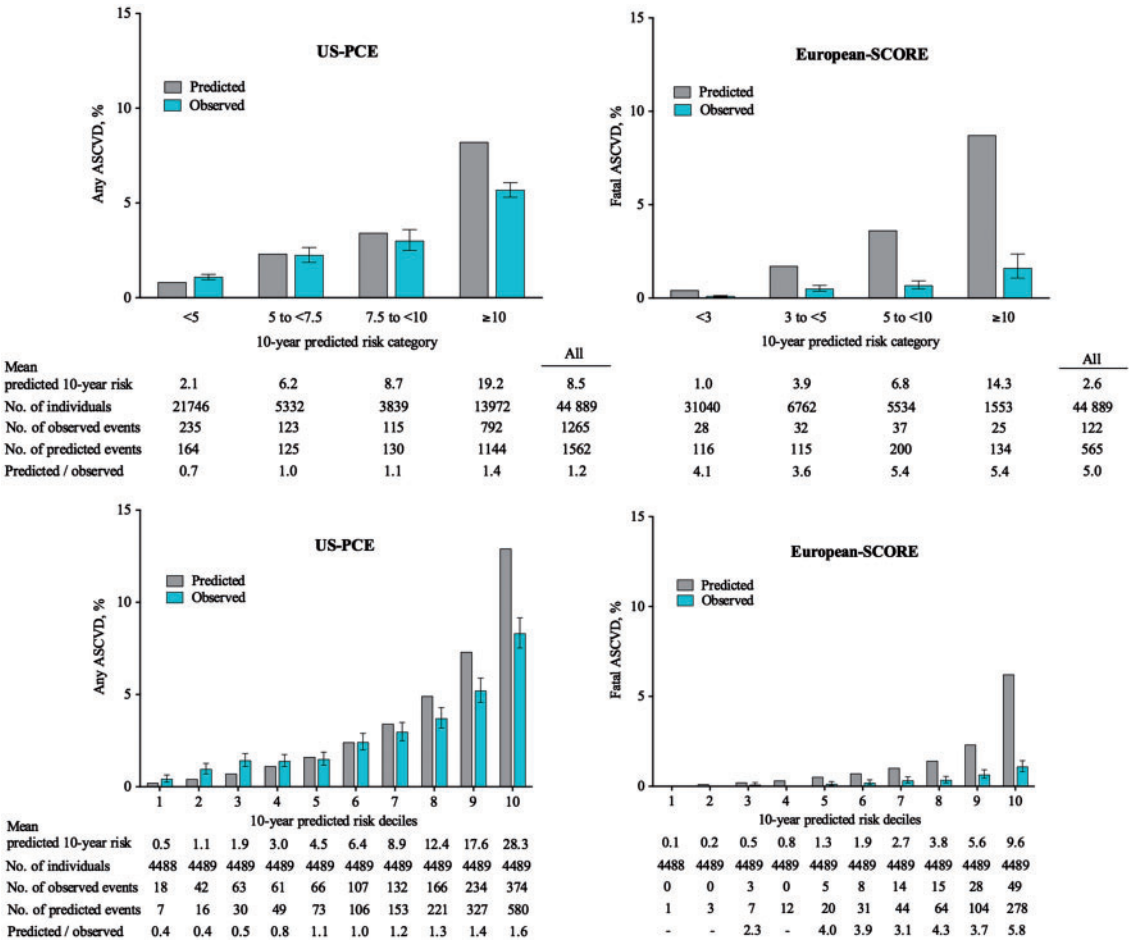
Prevention received a lot of attention during the last year. Not only were the ESC/EAS Guidelines on Prevention[1] and the Joint ESC/EAS Guidelines for the Management of Dyslipidaemias[2] published, but novel and most promising drugs for lipid disorders[3–5] and diabetes[6,7] were evaluated and discussed. Massimo F. Piepoli and colleagues from G. da Saliceto Hospital in Piacenza, Italy summarize in their review '**The year in cardiology 2016: prevention**'[8] the recent insights which have become available in the complex interaction between prevention and risk factor control. This includes healthy lifestyle, diet, smoking habit, obesity, diabetes, lipids, and hypertension. Furthermore, the pivotal role of environmental stressors such as noise and pollution is highlighted. Of the utmost importance was the introduction of novel, highly promising drugs such as the PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors for patients with hyperlipidaemia and of the inhibitors of the sodium–glucose exchanger for patients with diabetes.

An important novel topic in prevention is highlighted by Thomas Münzel and colleagues from the Johannes Gutenberg University in Mainz, Germany in a subsequent two-part clinical review article entitled '**Environmental stressors and cardio-metabolic disease**'.[9,10] The authors note that traffic noise[11] and air pollution together represent the two most important environmental risk factors in urbanized societies. The first of this two-part review discusses the epidemiological evidence in support of the existence of an association between these risk factors and cardiovascular and metabolic disease, as well as Tako Tsubo.[12] While independent effects of these risk factors have now clearly been shown, recent studies also suggest that the two exposures may interact with each other, and also with traditional risk factors such as hypertension and type 2 diabetes. From a societal and policy perspective, the health effects of both air pollution and traffic noise are observed for exposures well below the thresholds currently accepted as being safe. Current gaps in knowledge, effects of intervention, and their impact on cardiovascular disease are discussed in the second part of this review. Increased awareness of the societal burden posed by these novel risk factors and acknowledgement in traditional risk factor guidelines may intensify the efforts required for effective legislation to reduce air pollution and noise.

The novel PCSK9 inhibitors are both effective and expensive. Thus, their prescription must be considered by weighing costs and benefits.[13] In most countries, however, the cost of these drugs is only reimbursed for patients with familial hypercholesterolaemia. Hence, genetic testing in such individuals has become important. Joost Besseling and colleagues from the Academic Medical Center in Amsterdam, The Netherlands address this issue in their manuscript '**Selection of individuals for genetic testing for familial hypercholesterolaemia: development and external validation of a prediction model for the presence of a mutation causing familial hypercholesterolaemia**'.[14] The authors remind us that familial hypercholesterolaemia is an autosomal dominant disease that warrants early diagnosis to prevent premature cardiovascular disease. Genetic testing to make a definite diagnosis is costly, and careful selection of eligible subjects is important. Unfortunately, accuracy of current diagnostic criteria is poor, especially in young individuals. The authors therefore developed and validated a model to predict the presence of familial hypercholesterolaemia-causing mutations in persons referred by general practitioners. All participants in the Dutch familial hypercholesterolaemia screening programme from 1994 to 2014 were included in the development cohort. The validation cohort consisted of consecutive patients suspected of familial hypercholesterolaemia who were attending the outpatient lipid clinic in Saguenay in Quebec between 1993 and 2014. Cross-sectional data were available on medical history, lipid profile, and DNA analysis. Multivariable logistic regression analysis was used for model development. The primary outcome was the presence of a deleterious familial hypercholesterolaemia mutation. The development cohort comprised 26 167 familial hypercholesterolaemia patients and 37 939 unaffected relatives. The author's final model included age, gender, levels of LDL-cholesterol, HDL-cholesterol, and triglycerides, history and age of onset of cardiovascular disease, use of statins, smoking, alcohol, and presence of hypertension. The area under the receiver operating characteristic curve or AUC was 85%. The calibration slope was 1.02 (where 1.00 is optimal). In the validation cohort consisting of 1436 familial hypercholesterolaemia patients and 1767 unaffected individuals, the AUC was 95% and the calibration slope 1.06. The authors therefore conclude that their model allows for good discrimination and calibration and hence may be of particular added value for the prediction of a genetic mutation in young individuals. Their findings are discussed in a thought-provoking **Editorial** by Marina Cuchel from the University of Pennsylvania, USA.[15]



	<5	5 to <7.5	7.5 to <10	≥10	All
Mean predicted 10-year risk	2.1	6.2	8.7	19.2	8.5
No. of individuals	21746	5332	3839	13972	44 889
No. of observed events	235	123	115	792	1265
No. of predicted events	164	125	130	1144	1562
Predicted / observed	0.7	1.0	1.1	1.4	1.2

	<3	3 to <5	5 to <10	≥10	All
Mean predicted 10-year risk	1.0	3.9	6.8	14.3	2.6
No. of individuals	31040	6762	5534	1553	44 889
No. of observed events	28	32	37	25	122
No. of predicted events	116	115	200	134	565
Predicted / observed	4.1	3.6	5.4	5.4	5.0

	1	2	3	4	5	6	7	8	9	10
Mean predicted 10-year risk	0.5	1.1	1.9	3.0	4.5	6.4	8.9	12.4	17.6	28.3
No. of individuals	4488	4489	4489	4489	4489	4489	4489	4489	4489	4489
No. of observed events	18	42	63	61	66	107	132	166	234	374
No. of predicted events	7	16	30	49	73	106	153	221	327	580
Predicted / observed	0.4	0.4	0.5	0.8	1.1	1.0	1.2	1.3	1.4	1.6

	1	2	3	4	5	6	7	8	9	10
	0.1	0.2	0.5	0.8	1.3	1.9	2.7	3.8	5.6	9.6
	4488	4489	4489	4489	4489	4489	4489	4489	4489	4489
	0	0	3	0	5	8	14	15	28	49
	1	3	7	12	20	31	44	64	104	278
	-	-	2.3	-	4.0	3.9	3.1	4.3	3.7	5.8

Figure 1 Calibration comparing observed and predicted events in 40- to 75-year-old individuals in the Copenhagen General Population Study. US PCE performed well below 10% any atherosclerotic cardiovascular disease 10-year risk, with good calibration around the guideline-defined decision thresholds of 5% and 7.5% for statin therapy (left panel). In contrast, European SCORE overestimated risk across all deciles and categories of fatal atherosclerotic cardiovascular disease 10-year predicted risk, with substantial overestimation around both the high-risk (5%) and very-high-risk (10%) thresholds for statin therapy (right panel). Observed events were Kaplan–Meier adjusted. Error bars indicate 95% confidence interval. PCE, pooled cohort equations; SCORE, SystematicCOronary Risk Evaluation. (from Mortensen MB, Nordestgaard BG, Afzal S, Falk E. ACC/AHA guidelines superior to ESC/EAS guidelines for primary prevention with statins in non-diabetic Europeans: the Copenhagen General Population Study. See pages 586–594.)

While the untoward effects of cardiometabolic risk factors on the heart and the peripheral circulation are well established, their effects on the brain and in particular on cognitive function are less well characterized, although in heart failure cognitive impairment seems to be associated with outcome.[16] In their manuscript entitled '**Associations between single and multiple cardiometabolic diseases and cognitive abilities in 474 129 UK Biobank participants**',[17] Donald Lyall and colleagues from the University of Glasgow in the UK investigated this aspect. Indeed, cardiometabolic diseases such as hypertension, coronary artery disease, and type 2 diabetes are known to associate with poorer cognitive ability but there are limited data on whether having more than one of these conditions is associated with additive effects. The authors aimed to quantify the magnitude of their associations with non-demented cognitive abilities, and to determine the extent to which these associations were additive. To that end, they obtained cognitive test scores in domains of reasoning, information processing speed, and memory, included as part of the baseline UK Biobank cohort assessment in 474 129 individuals and adjusted for a range of potentially confounding variables. Hypertension, coronary artery disease, and type 2 diabetes was generally associated with poorer cognitive scores on all tests, compared with a control group that reported none of these diseases. There was evidence of an additive deleterious dose effect of an increasing number of cardiometabolic diseases, for reasoning scores and log memory errors. The authors therefore concluded that cardiometabolic diseases are associated with worse cognitive abilities, and the effect of an increasing number of cardiometabolic conditions appears additive. These results reinforce the notion that

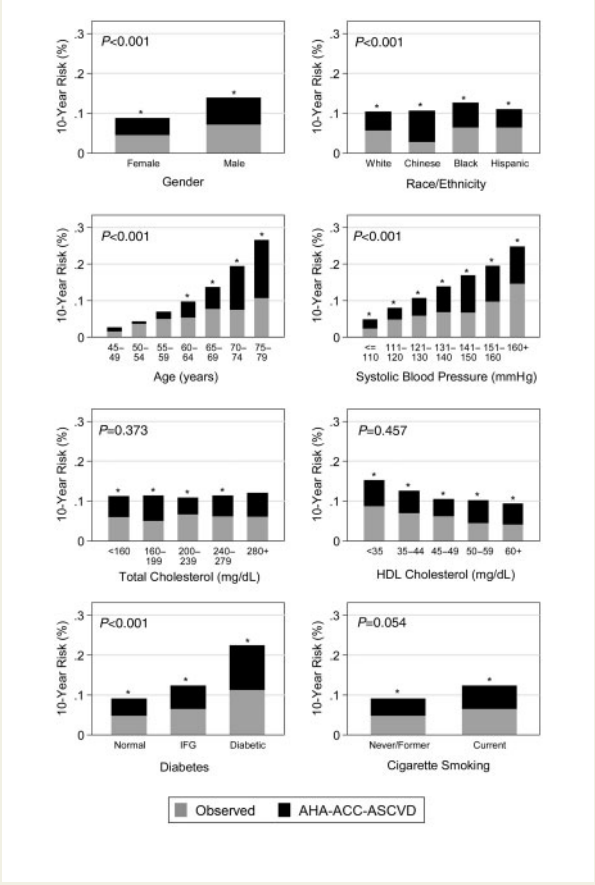


Figure 2 Observed atherosclerotic cardiovascular disease percentage and American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score predicted percentage. *P-value of ,0.05 for proportion test comparing American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease predicted risk (total height of each bar) with the observed risk in Multi-Ethnic Study of Atherosclerosis (grey portion of bars). For example, the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease predicted risk for men was 13.9%, whereas the observed rate was 7.2%, and a two-tailed test of proportions showed these rates were significantly different at the 95% level. Reported P-value compares the overestimation (i.e. the black bars) for each risk factor. For example, the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease predicted risk (total height of each bar) was higher than the observed risk (grey portion of the bar) for females and for males, and the overestimation for males was significantly greater (P , 0.001) than the overestimation for females. P-values come from an absolute risk regression model, which is a linear regression model at the individual level, predicting a dichotomous outcome (atherosclerotic cardiovascular disease event yes/no within 10 years). It was fit as a generalized linear model with the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score entered as an offset (fixing the coefficient to 1.0), with an identity link function and using robust standard errors. To this model, we added each risk factor separately. P-value for race/ethnicity categories shows joint F-test of significance. (from DeFilippis AP, Young R, McEvoy JW, Michos ED, Sandfort V, Kronmal RA, McClelland RL, Blaha MJ. Risk score overestimation: the impact of individual cardiovascular risk

preventing or delaying cardiovascular disease or diabetes may also delay cognitive decline and possibly dementia. These clinically important findings are put into context in an **Editorial** authored by Jack de la Torre from the University of Texas at Austin, USA.[18]

Risk scores are essential tools in the prevention of cardiovascular disease and the basis of many guideline recommendations. To that end, a large number of scores have been developed by different professional societies. Rarely have they been evaluated head-to-head to determine their true clinical value. In their research article, '**ACC/AHA guidelines superior to ESC/EAS guidelines for primary prevention with statins in non-diabetic Europeans: the Copenhagen General Population Study**',[19] Børge Grønne Nordestgaard and colleagues from the Herlev University Hospital in Denmark compared the 2013 American College of Cardiology/American Heart Association or ACC/AHA[20] and the 2012 European Society of Cardiology/European Atherosclerosis Society or ESC/EAS guidelines on prevention of atherosclerotic cardiovascular disease[21] using different risk prediction models such as the US Pooled Cohort Equations or US-PCE, a score predicting any event, and the European Systematic COronary Risk Evaluation system or European-SCORE that predicts only fatal events and different statin eligibility criteria. The authors examined 44 889 individuals aged 40–75 recruited in the Copenhagen General Population Study, all free of cardiovascular disease and diabetes, and off statin use at baseline. They detected 2217 atherosclerotic cardiovascular events and 199 fatal events. The predicted-to-observed event ratio was 1.2 using US-PCE for any event and 5.0 using European-SCORE for fatal events. The US-PCE, but not the European-SCORE, was well calibrated around decision thresholds for statin therapy (*Figure 1*). Indeed, for a class I recommendation, 42% of individuals qualified for statins using the ACC/AHA guidelines, but only 6% using the ESC/EAS guidelines. Using ACC/AHA- vs. ESC/EAS-defined statin eligibility criteria led to a substantial gain in sensitivity of 62% for any event and 76% for fatal events, with a smaller loss in specificity of 35% for any and 36% for fatal atherosclerotic events. Similar differences between the ACC/AHA and ESC/EAS guidelines were found for men and women separately, and for class IIa recommendations. The sensitivity and specificity of a US-PCE risk of 5% were similar to those of a European-SCORE risk of 1.4%, while a US-PCE risk of 7.5% was similar to a European-SCORE risk of 2.4% (*Figure 2*). Nordestgaard and collegues conclude that the ACC/AHA guidelines were superior to the ESC/EAS guidelines for primary prevention of atherosclerotic cardiovascular disease, specifically for assigning statin therapy to those who would benefit the most. These provocative findings are put into perspective in an **Editorial** by John J.P. Kastelein from the University of Amsterdam in The Netherlands.[22]

This approach is further refined in a final research article **'Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the AHA-ACC-ASCVD risk scores in a modern**

factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. See pages 598–608.)

multiethnic cohort' by Andrew Paul DeFilippis and colleagues from the University of Louisville in Kentucky, USA.[23] The authors evaluated the 2013 American Heart Association (AHA)–American College of Cardiology (ACC)-Atherosclerotic Cardiovascular Disease or ASCVD risk score among different race or ethnic groups, specifically to ascertain which factors are most associated with risk overestimation by the AHA-ACC-ASCVD scores. The Multi-Ethnic Study of Atherosclerosis, called MESA, a prospective community-based cohort, was used to examine calibration and discrimination of the AHA-ACC-ASCVD risk score in 6441 White, Black, Chinese, and Hispanic Americans, aged 45–79 years, free of known cardiovascular disease at baseline. Overestimation of risk was observed in all race and ethnic groups in MESA and was highest among Chinese, with 252% for women and 314% for men and lowest in White women with 72% and Hispanic men with 67% overestimation, respectively. Higher age, Chinese ethnicity as compared with Whites, systolic blood pressure, regardless of whether treated or untreated, diabetes, alcohol use, exercise, lipid-lowering medication, and aspirin use were all associated with a greater risk overestimation, while family history was associated with less. The authors conclude that the AHA-ACC-ASCVD risk score overestimates atherosclerotic cardiovascular risk among men, women, and in all four race or ethnic groups evaluated in a modern US primary prevention cohort. Clinicians treating patients similar to those in MESA, particularly older individuals and those with factors associated with more risk overestimation, should therefore consider interpreting absolute ASCVD risk estimates with caution.

The editors hope that readers of this issue of the *European Heart Journal* will find it of interest.

References

1. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM; Authors/Task Force Members. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
2. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL; Authors/Task Force Members; Additional Contributors. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J* 2016;**37**:2999–3058.
3. Lipinski MJ, Benedetto U, Escarcega RO, Biondi-Zoccai G, Lhermusier T, Baker NC, Torguson R, Brewer HB Jr, Waksman R. The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis. *Eur Heart J* 2016;**37**:536–545.
4. Kastelein JJ, Nissen SE, Rader DJ, Hovingh GK, Wang MD, Shen T, Krueger KA. Safety and efficacy of LY3015014, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9): a randomized, placebo-controlled Phase 2 study. *Eur Heart J* 2016;**37**:1360–2369.
5. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, Koenig W, Somaratne R, Kassahun H, Yang J, Wasserman SM, Scott R, Ungi I, Podolec J, Ophuis AO, Cornel JH, Borgman M, Brennan DM, Nissen SE. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. *JAMA* 2016;**316**:2373–2384.
6. Marx N, McGuire DK. Sodium–glucose cotransporter-2 inhibition for the reduction of cardiovascular events in high-risk patients with diabetes mellitus. *Eur Heart J* 2016;**37**:3192–3200.
7. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME® trial investigators. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. *Eur Heart J* 2016;**37**:1526–1534.
8. Piepoli MF, Taddei S, Laufs U. The year in cardiology 2016: prevention. *Eur Heart J* 2017;**38**:542–549.
9. Münzel T, Sørensen M, Gori T, Schmidt FP, Rao X, Brook J, Chen LC, Brook RD, Rajagopalan S. Environmental stressors and cardio-metabolic disease: part I-epidemiological evidence supporting a role for noise and air pollution and effects of mitigation strategies. *Eur Heart J* 2017;**38**:550–556.
10. Munzel T, Sørensen M, Gori T, Schmidt FP, Rao X, Brook FR, Chen LC, Brook RD, Rajagopalan S. Environmental stressors and cardio-metabolic disease: part II—mechanistic insights. *Eur Heart J* 2017;**38**:557–564.
11. Halonen JI, Hansell AL, Gulliver J, Morley D, Blangiardo M, Fecht D, Toledano MB, Beevers SD, Anderson HR, Kelly FJ, Tonne C. Road traffic noise is associated with increased cardiovascular morbidity and mortality and all-cause mortality in London. *Eur Heart J* 2015;**36**:2653–2661.
12. Munzel T, Knorr M, Schmidt F, von Bardeleben S, Gori T, Schulz E. Airborne disease: a case of a Takotsubo cardiomyopathie as a consequence of nighttime aircraft noise exposure. *Eur Heart J* 2016;**37**:2844.
13. Landmesser U, John Chapman M, Farnier M, Gencer B, Gielen S, Hovingh GK, Lüscher TF, Sinning D, Tokgözoğlu L, Wiklund O, Zamorano JL, Pinto FJ, Catapano AL; European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk. *Eur Heart J* 2016;doi:10.1093/eurheartj/ehw480.
14. Besseling J, Reitsma JB, Gaudet D, Brisson D, Kastelein JJP, Hovingh GK, Huttern BA. Selection of individuals for genetic testing for familial hypercholesterolaemia: development and external validation of a prediction model for the presence of a mutation causing familial hypercholesterolaemia. *Eur Heart J* 2017;**38**:565–573.
15. Ajufo E, Cuchel M. Improving the yield of genetic testing in familial hypercholesterolaemia. *Eur Heart J* 2017;**38**:574–576.
16. Taylor J. Cognitive impairment predicts worse outcome in heart failure. *Eur Heart J* 2015;**36**:1945.
17. Lyall DM, Celis-Morales CA, Anderson J, Gill JMR, Mackay DF, McIntosh AM, Smith DJ, Deary IJ, Sattar N, Pell JP. Associations between single and multiple cardiometabolic diseases and cognitive abilities in 474 129 UK Biobank participants. *Eur Heart J* 2017;**38**:577–583.
18. de la Torre JC. Cardiac dysfunction and cognitive decline. *Eur Heart J* 2017;**38**:584–585.
19. Mortensen MB, Nordestgaard BG, Afzal S, Falk E. ACC/AHA guidelines superior to ESC/EAS guidelines for primary prevention with statins in non-diabetic Europeans: the Copenhagen General Population Study. *Eur Heart J* 2017;**38**:586–594.
20. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Sorlie P, Stone NJ, Wilson PWF. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. *Circulation* 2013;01.cir.0000437741.4.
21. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;**33**:1635–1701.
22. Ray KK, Kastelein JJP. Time to change the SCORE? *Eur Heart J* 2017;**38**:595–597.
23. DeFilippis AP, Young R, McEvoy JW, Michos ED, Sandfort V, Kronmal RA, McClelland RL, Blaha MJ. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. *Eur Heart J* 2017;**38**:598–608.