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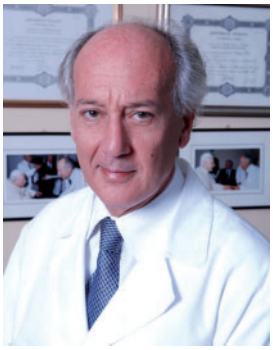
The ESC Guidelines on cardiovascular prevention and a focus on old and new risk factors



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This Focus Issue on epidemiology and prevention contains the '**2021 ESC Guidelines on cardiovascular disease prevention in clinical practice**'.[1] The present guidelines concentrate principally, but not exclusively, on the risk factors, risk classification, and prevention of atherosclerotic cardiovascular disease (ASCVD). Special considerations have been given to differences in age, sex, and gender, life expectancy, risk factor profiles, and ethnic and geographic differences. 'Residual' cardiovascular disease (CVD) risk is defined as the risk estimated after initial lifestyle changes and risk factor treatment, and is mostly used in patients with established ASCVD. For younger apparently healthy subjects, lifetime CVD risk estimates are available to support treatment decisions, replacing 10-year risk algorithms that consistently estimate low 10-year risk even in the presence of high-risk factor levels, while in an ageing population, treatment decisions require a specific CVD risk score that takes competing non-CVD risk into account. Estimating lifetime benefit in individual patients of smoking cessation, LDL-cholesterol lowering, and blood pressure lowering provides opportunities to communicate benefit of treatment in an easy-to-understand way. Personalized treatment decisions using CVD risk estimations and a stepwise approach to treatment is more complex than a more general one size fits all prevention strategy, but reflects the diversity in patients and patient characteristics in clinical practice. These guidelines propose a new, stepwise approach to treatment intensification as a tool to help physicians and patients pursue these targets in a way that fits the patient profile and preferences. New evidence on antithrombotic treatment regimens for ASCVD prevention is also presented. Sex-specific aspects are included. ASCVD prevention needs an integrated, interdisciplinary approach including input from several disciplines and areas of expertise.

In a State of the Art Review article entitled '**Persisting burden and challenges of rheumatic heart disease**', Eloi Marijon from the University of Paris in France, and colleagues note that rheumatic heart disease (RHD) is the result of episodes of acute rheumatic fever, with valvular (and other cardiac) damage caused by an abnormal immune response to group A streptococcal (GAS) infections, usually during childhood and adolescence.[2] As a result of improved living conditions and the introduction of penicillin, RHD was almost eradicated in the developed world by the 1980s. However, being a disease of poverty, its burden remains disproportionately high in the developing world, despite being a fundamentally preventable disease. RHD generates relatively little attention from the medical and science communities, in contrast to other common infectious problems (such as malaria, HIV, or tuberculosis),[3] despite the major cardiovascular morbidity/mortality burden imposed by RHD. This relative neglect and paucity of funding has probably contributed to limited fundamental medical advances in this field for over 50 years.

Observational studies have suggested strong associations between sleep duration and CVD risk, but causal inferences have not been confirmed.[4–6] In a Clinical Research contribution entitled '**Causal associations of short and long sleep durations with 12 cardiovascular diseases: linear and non-linear Mendelian randomization analyses in UK Biobank**', Sizhi Ai from the Chinese University of Hong Kong in China, and colleagues sought to determine the causal associations between genetically predicted sleep duration and CVDs using both linear and non-linear Mendelian randomization (MR) designs.[7] Genetic variants associated with continuous, short (≤6 h) and long (≥9 h) sleep durations were used to examine the causal associations with 12 CVDs among >400 000 UK Biobank participants of White British ancestry. Linear and non-linear MR analyses showed that the genetically predicted sleep duration was negatively associated with arterial hypertension, atrial fibrillation, pulmonary embolism, myocardial infarction, and chronic ischaemic heart disease after correcting for multiple tests ($P < 0.001$). In sharp contrast, genetically predicted long sleep duration was not associated with any CVD (*Figure 1*).

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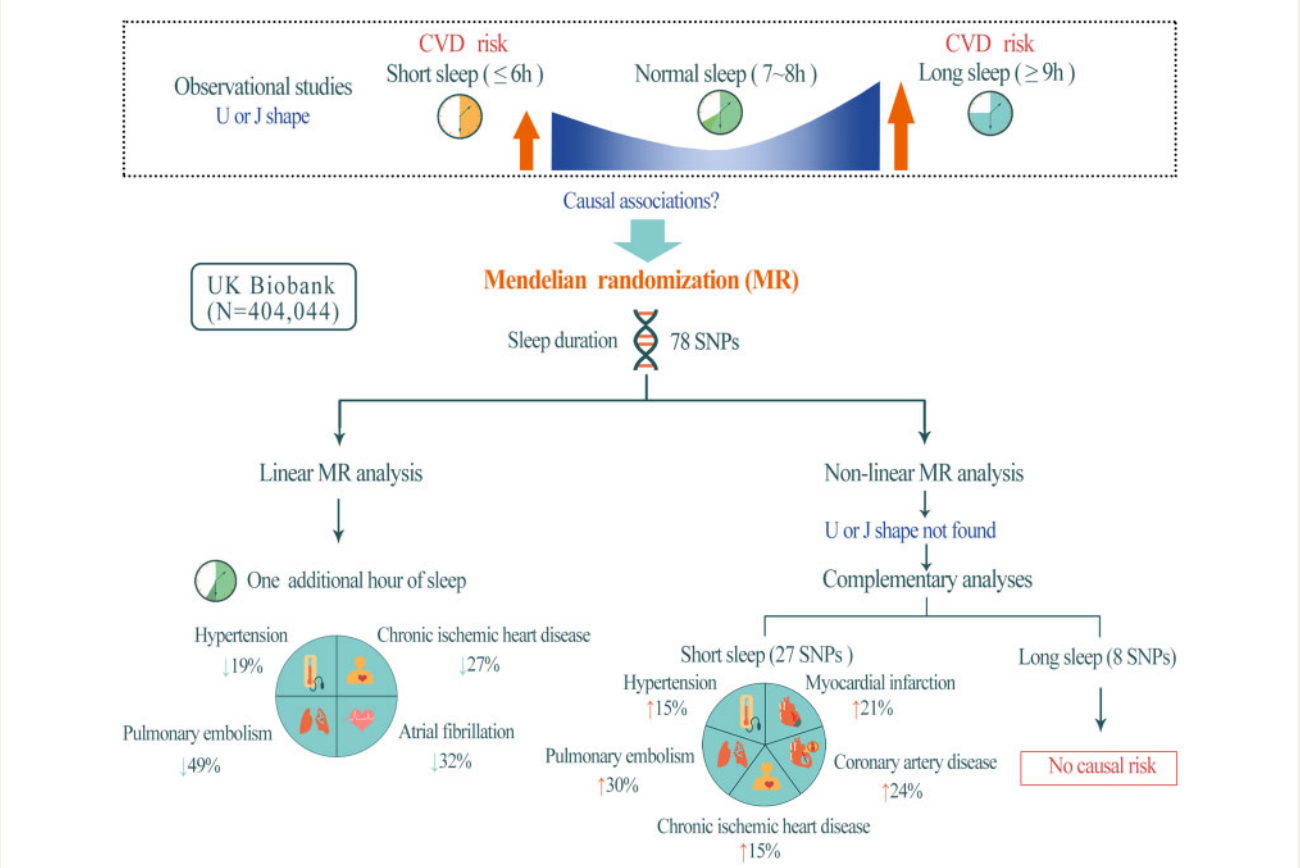

Figure 1 Causal associations of short and long sleep durations with 12 cardiovascular diseases: linear and non-linear Mendelian randomization analyses in the UK Biobank. All associations are significant at a Bonferroni threshold of $P < 4.2E-03$ (corrected for 12 outcomes). CVD, cardiovascular disease; SNP, single nucleotide polymorphism (from Ai S, Zhang J, Zhao G, Wang N, Li G, So HC, Liu Y, Chau SW, Chen J, Tan X, Jia F, Tang X, Shi J, Lu L, Wing YK. Causal associations of short and long sleep durations with 12 cardiovascular diseases: linear and non-linear Mendelian randomization analyses in UK Biobank. See pages 3349–3357).

The authors conclude that their study suggests that genetically predicted short sleep duration is a potential causal risk factor of several CVDs, while genetically predicted long sleep duration is unlikely to be a causal risk factor for most CVDs. The manuscript is accompanied by an **Editorial** by Susan Redline and colleagues from Harvard Medical School in Boston, MA, USA.[4] The authors note that while MR is uniquely appropriate for studying causal associations, relying on genetic variants determined at birth, it also has some limitations, e.g. because genetic variants may have pleiotropic associations with the outcome, and because it is not immune to selection bias. There are opportunities to better characterize the causal relationship between sleep duration and CVD using additional causal inference methods, and, importantly, to expand those analyses to diverse populations. Finally, the mounting evidence of a causal association of sleep duration and CVD should motivate follow-up investigation of specific mechanisms behind the association, development of biomarkers, and studies of effective clinical and behavioural interventions.

Among the current efforts to reduce the mortality from cardiometabolic diseases is the identification and preventive treatment of high-risk individuals. However, identification of individuals with a high risk for cardiometabolic disease is challenging even when accounting for multiple risk factors such as obesity, hypertension, diet, smoking, air pollution, and lack of physical activity.[8–10] In addition, the established risk prediction algorithms are usually specific for certain age, sex, and ethnic groups, and may over- or underestimate the risk in other groups. In recent years, microcalcifications identified in routine mammograms were found to be associated with cardiometabolic disease in women. In a Clinical Research article entitled '**Mammographic features are associated with cardiometabolic disease risk and mortality**', Felix Grassmann from the Karolinska Institutet in Stockholm, Sweden, and colleagues aimed to systematically evaluate the association of microcalcifications and other mammographic features with cardiometabolic disease risk and mortality in a large screening cohort and to understand a potential genetic contribution.[11] This study included ~58 000 women from a prospective mammographic screening cohort in Sweden (KARMA) and ~50 000 of their sisters. Cardiometabolic disease diagnoses and mortality as well as medication were extracted by linkage to Swedish population registries, with virtually no missing data. In the cardiometabolic phenome-wide association study, the authors found that a higher number of microcalcifications was associated with increased risk for

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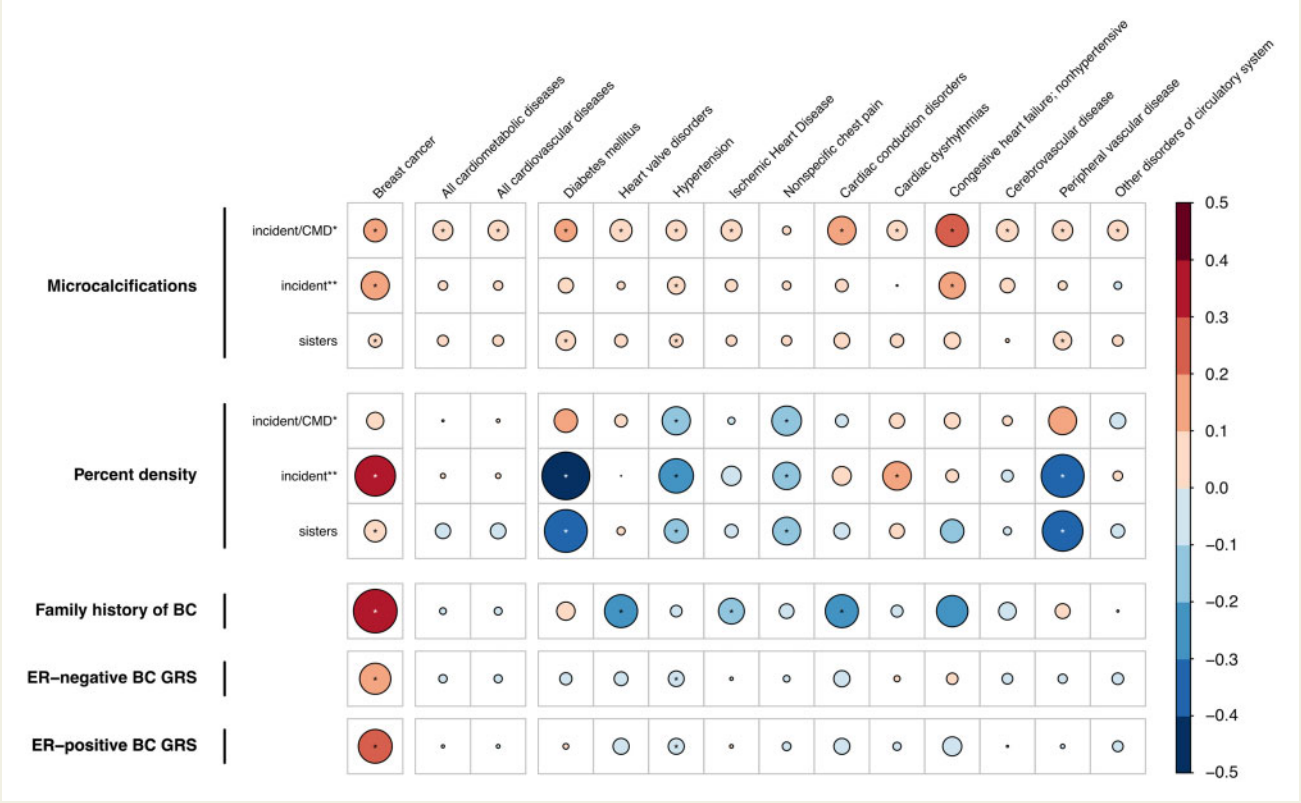

Figure 2 Graphical Abstract (from Grassmann F, Yang H, Eriksson M, Azam S, Hall P, Czene K. Mammographic features are associated with cardiometabolic disease risk and mortality. See pages 3361–3370).

multiple cardiometabolic diseases, particularly in women with pre-existing cardiometabolic diseases. In sharp contrast, higher breast density associated with a lower incidence of cardiometabolic diseases. Importantly, they observed similar associations in sisters of KARMA women, indicating a potential genetic overlap between mammographic features and cardiometabolic traits (*Figure 2*).

Grassmann *et al.* conclude that they demonstrate that mammographic features are associated with cardiometabolic risk and mortality. The results strengthen the notion that a combination of mammographic features and other breast cancer risk factors could be a novel and affordable tool to assess cardiometabolic health in women attending mammographic screening. This manuscript is accompanied by an **Editorial** by Angela H.E.M. Maas from the Radboudumc in Nijmegen, the Netherlands.[12] She notes that we need to better understand what we measure on a mammogram. This means a movement away from the number of clusters of unknown microcalcifications towards an automated dedicated measurement of ductal microcalcification. Such an 'Agatston score for mammography' could turn the promising but weak signals into more powerful absolute risk predictors and identify women at risk in order to prevent adverse cardiovascular outcomes.

In another Clinical Research article entitled '**Lifestyle, cardiometabolic disease, and multimorbidity in a prospective Chinese study**', Yuting Han from the Peking University in China, and colleagues note that the potential difference in the impact of lifestyle factors (LFs) on progression from healthy to first cardiometabolic disease (FCMD), subsequently to cardiometabolic multimorbidity (CMM), and further to death is unclear.[13] The authors used data from the China Kadoorie Biobank of >460 000 adults aged 30–79 free of heart disease, stroke, and diabetes at baseline. CMM was defined as the co-existence of two or three CMDs, including ischaemic heart disease (IHD), stroke, and type 2 diabetes (T2D). The authors used a multistate model to analyse the impact of high-risk LFs (current smoking or quitting because of illness, current excessive alcohol drinking or quitting, poor diet, physical inactivity, and unhealthy body shape) on the progression of CMD. During a median follow-up of 11.2 years, >87 000 participants developed at least one CMD, >14 000 developed CMM, and >17 000 died afterward. Five high-risk LFs played crucial but different roles in all transitions from healthy to FCMD, to CMM, and then to death. When they further divided FCMDs into IHD, ischaemic stroke, haemorrhagic stroke, and T2D, they found that LFs played different roles in disease-specific transitions even within the same transition stage.

Han *et al.* conclude that their findings emphasize the importance of integrating comprehensive lifestyle interventions into both health management and CMD management. The contribution is accompanied by an **Editorial** by Dong Zhao from the Capital Medical University Beijing Anzhen Hospital in China.[14] Dr Zhao states that the findings of this study provide evidence showing the importance of lifestyle intervention in primary and secondary prevention of CMD in

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China. These findings also imply that the residual risk of CVD among well-treated people in primary and secondary prevention may be partly from the lasting effects from unhealthy lifestyle risk factors. This study also provides useful information for providing health education to the population and to patients with CMD.

The pandemic of obesity around the globe is raising growing concern.[13,15,16] In a meta-analysis article '**Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies**' Min Seo Kim from the Korea University in the Republic of Korea, and colleagues investigated the causal relationship and evidence of an association between increased adiposity and the risk of incident CVD or mortality.[17] Observational (informing association) and MR (informing causality) studies were assessed to gather mutually complementary insights and elucidate perplexing epidemiological relationships. Systematic reviews and meta-analyses of observational and MR studies that were published up to January 2021 were examined, and the association between obesity-related indices and CVD risk was searched. Twelve systematic reviews with results from 53 meta-analyses (including >501 cohort studies) and 12 MR studies were included in the analysis. A body mass index (BMI) increase was associated with higher risks of coronary heart disease, heart failure, atrial fibrillation, all-cause stroke, haemorrhagic stroke, ischaemic stroke, hypertension, aortic valve stenosis, pulmonary embolism, and venous thrombo-embolism. The MR study results demonstrated a causal effect of obesity on all indices except stroke. The CVD risk increase for every 5 kg/m^2 increase in BMI varied from 10% for haemorrhagic stroke to 49% for hypertension. The all-cause and CVD-specific mortality risks increased with adiposity in cohorts, but the MR studies demonstrated no causal effect of adiposity on all-cause mortality.

The authors conclude that high adiposity is associated with increased CVD risk despite divergent evidence gradients. Adiposity is a causal risk factor for CVD except all-cause mortality and stroke. The associations are consistent between sexes and across regions. This study provides guidance on how to integrate evidence from observational (association) and genetics-driven (causation) studies accumulated to date, to enable a more reliable interpretation of epidemiological relationships. The manuscript is accompanied by an **Editorial** by Annika Rosengren from the University of Gothenburg Institute of Medicine in Sweden.[18] The author concludes that the massive work undertaken in the study by Kim *et al.* is of particular interest for our understanding of current trends in heart disease incidence, and potentially also for what to expect in the future when increasing numbers of overweight, obese, and severely obese people who are now young, or adolescent, become middle aged and older. In a recent study from the USA, heart failure and hypertensive heart disease accounted for major increases in premature deaths and offset declines in ischaemic heart disease mortality. Similarly, in Sweden, a shift in young-onset CVD events (before the age of 40) in men demonstrated a marked shift from incident acute myocardial infarction to incident heart failure. The much lower effect size by continuous BMI on coronary heart disease relative to that of heart failure could help explain these emerging trends and provide some indication of what might happen in the future when heart failure, already a huge global issue in the elderly, will probably surpass acute myocardial infarction as a major problem also among the young and middle aged.

The issue is also complemented by two Discussion Forum contributions. In a commentary entitled '**Clinical and methodological considerations when interpreting meta-analyses of beta-blocker use in patients with chronic obstructive pulmonary disease**', Claudia Gulea from the Imperial College London in the UK, and colleagues comment on the recent publication '**Association of β-blocker use with survival and pulmonary function in patients with chronic obstructive pulmonary and cardiovascular disease: a systematic review and meta-analysis**' by Yan-Li Yang from the Peking Union Medical College Hospital in Beijing, China.[19,20] Yang *et al.* respond in a separate comment.[21]

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

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