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The metabolic syndrome – What is it and how should it be managed?

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Abstract

A cluster of metabolic factors have been merged into an entity named the metabolic syndrome. Although the characteristics of this syndrome have varied over time the presently used definition was established in 2009. The presence of three abnormal findings out of five components qualifies a person for the metabolic syndrome: elevated waist circumference, elevated triglycerides, reduced high-density lipoprotein cholesterol, elevated blood pressure and elevated fasting plasma glucose. Cut points have been defined for all components apart from waist circumference, for which national or regional values are used. The metabolic syndrome predicts cardiovascular disease and type 2 diabetes. This associated risk does not exceed its components whereof elevated blood pressure is the most frequent. A successful management should, however, address all factors involved. The management is always based on healthy lifestyle choices but has not infrequently to be supported by pharmacological treatment, especially blood pressure lowering drugs. The metabolic syndrome is a useful example of the importance of multiple targets for preventive interventions. To be successful management has to be individualized not the least when it comes to pharmacological therapy. Frail elderly people should not be over-treated. Knowledge transfer of how risk factors act should be accompanied by continuous trust building and motivation. In complex situations with a mix of biological risk factors, adverse social conditions and unhealthy lifestyle, everything cannot be changed at once. It is better to aim for small steps that are lasting than large, unsustainable steps with relapses to unhealthy behaviours. A person with the metabolic syndrome will always be afflicted by its components, which is the reason that management has to be sustained over a very long time. This review summarizes the knowledge on the metabolic syndrome and its management according to present state of the art.

Keywords

Cardiovascular risk, risk for type 2 diabetes, plasma glucose, blood pressure, waist circumference, blood lipids, lifestyle, dietary habits, physical activity

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Introduction

The word ‘syndrome’ originates from the Greek ‘σύνδρομον’, with the meaning ‘coexistence’. In the medical context it is used to describe a cluster of signs and symptoms that in one way or another are related to a certain disease.[1] Sometimes the term ‘syndrome’ may be so closely connected to the pathophysiological process behind a disease that it is difficult to separate the two from each other, syndrome and disease, and an example may be Down’s syndrome. More commonly, however, a syndrome indicates that certain clinical findings co-exist more frequently than would be expected if it was just a play of chance and that this accumulation is of clinical relevance. Still, the cause may often be uncertain. The metabolic syndrome represents such an entity and its presence signals that a person with this syndrome is at an increased risk for developing type 2 diabetes (T2D) and cardiovascular disease in the future and that such a dismal outcome may be counteracted

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by managing the components of the metabolic syndrome by means of appropriate measures.[2]

The objective of this review is to (1) give an historical background to the metabolic syndrome, (2) describe how its components were harmonized in 2009, (3) report on the clinical implications of the syndrome, and (4) review how the syndrome should be managed according to the state of the clinical art in 2019.

Historical background to the metabolic syndrome

Various diagnostic criteria have been proposed by different people and organizations over the past decades. In 1923 the Swedish physician Kylin published a scientific article in which he described a cluster of hyperuricaemia, hyperglycaemia and hypertension.[3] His observation was, however, not followed up. In 1947 the French physician Vague outlined two different types of obesity: abdominal adiposity (masculine type) and lower body adiposity (female type). He emphasized that it is abdominal adiposity that was associated with cardiovascular disease and T2D.[4] A further characterization was brought forward by Reaven in his Banting lecture in 1988 in which the cluster was considered related to insulin resistance; he labelled the cluster 'syndrome X'.[5] Kaplan called this combination of obesity, non-insulin-dependent diabetes mellitus, hypertension and dyslipidaemia 'the deadly quartet'.[6]

Since then, the syndrome evolved with different combinations of factors proposed to be included until in 1999 the World Health Organization (WHO) Consultation Group launched a definition based on central obesity combined with a cluster of metabolic abnormalities.[7] Insulin resistance was underlined as the major underlying risk factor and evidence of insulin resistance was required for the diagnosis. Thus, a diagnosis of the metabolic syndrome by WHO criteria necessitated markers of insulin resistance plus two additional risk factors, including obesity, hyperglycaemia, hypertension, high serum triglycerides, reduced serum high-density lipoprotein (HDL) cholesterol or microalbuminuria. Interestingly, people with T2D were not excluded from the definition but were considered as having elevated glucose concentration. Soon, several other definitions of the metabolic syndrome were published (Table 1).

The International Diabetes Federation (IDF) dropped the need for verified insulin resistance and made abdominal obesity necessary as one of five factors required for the diagnosis. Waist measurement was emphasized as a simple screening tool.[9] In 2001 in the United States the National Cholesterol Education Program Adult Treatment Panel III (ATP III) proposed its criteria, without a requirement of insulin resistance. The ATP III criteria used higher cut-points for waist circumference than other definitions in order to be consistent with the definitions of abdominal obesity by the National Institutes of Health (NIH) obesity guidelines.[10]

Researchers tried to agree upon a definition of the syndrome, its components and name, but this work just led to a plethora of publications on the epidemiology and clinical aspects of the metabolic syndrome in different populations and various sub-groups. The risk factors usually included raised blood pressure, dyslipidaemia (raised triglycerides and low HDL cholesterol), raised fasting plasma glucose, raised fasting serum insulin and obesity (central obesity defined as a large waist circumference or waist–hip ratio or body-mass index). The dyslipidaemia seen in the metabolic syndrome is characterized by large very-low-density-lipoprotein

Table 1. The 'harmonized' metabolic syndrome: criteria for clinical diagnosis (adapted from Borges et al.[8]).

Measure	Categorical cut-points
Elevated waist circumference	Population- and country-specific definitions
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L)
Drug treatment for elevated triglycerides is an alternative indicator	
Reduced HDL cholesterol	Males: <40 mg/dL (1.0 mmol/L)
Drug treatment for reduced HDL-C is an alternative indicator	Females: <50 mg/dL (1.3 mmol/L)
Elevated blood pressure	Systolic≥130 and/or
Antihypertensive drug treatment in patients with a history of hypertension is an alternative indicator	Diastolic≥85 mmHg
Elevated fasting plasma glucose	≥100 mg/dL (≥5.6 mmol/L)
Drug treatment of elevated glucose is an alternative criterion	

HDL-C: high-density lipoprotein cholesterol.

particles, which initiates the generation atherogenic remnants in the form of small dense low-density lipoprotein and small triglyceride-rich dense high-density lipoprotein particles, creating a highly atherogenic lipid profile.[11] Other factors were proposed as well. Hyperuricaemia, as originally pointed out by Kylin,[3] may be considered a part of the syndrome, more recently suggested also by other researchers.[8]

One important, albeit criticized, aspect of the metabolic syndrome is that its components are all continuous variables, including their associations with cardiovascular disease and T2D. Therefore dichotomizing them for the metabolic syndrome is arbitrary, resulting in false positives and many people being incorrectly labelled to be at risk of cardiovascular disease or T2D. There are commonly agreed international, evidence-based criteria for various risk factors. The cut-points adopted for the metabolic syndrome were, however, chosen for pragmatic reasons. One may also argue that people with any component of the metabolic syndrome are likely to benefit from a healthy lifestyle and therefore not mis-labelled.

Interestingly, Reaven critically reviewed the metabolic syndrome for lack of consistency of the components of the syndrome and their diagnostic criteria. He proposed cut-points including the number of components needed to make a diagnosis as suggested by different researchers.[12] He actually asked whether there was any reason why the metabolic syndrome should not be given its well-deserved send-off.

The 2009 harmonization of the metabolic syndrome

Since several definitions of the metabolic syndrome were proposed, it led to confusion as to how to identify the syndrome. Some controversy also existed about whether the metabolic syndrome is a true syndrome or a mixture of unrelated phenotypes.[13] Whether the metabolic syndrome fulfils the criteria of the true syndrome could only be assessed by well-designed scientific research. It was, however, recognized that the proposed metabolic syndrome was not an absolute risk indicator, because its definition did not contain many of the factors that determine cardiovascular risk, for example, age, sex, cigarette smoking, inflammation, apolipoprotein B or low-density lipoprotein cholesterol.

In 2009, representatives from IDF, American Heart Association, NIH, International Atherosclerosis Society, World Heart Federation and International Association for the Study of Obesity attempted to resolve the differences between definitions of metabolic syndrome. They came up with a proposal called 'harmonizing metabolic syndrome' with five components.[13] It was agreed that none of them should be obligatory, while three abnormal findings out of five components would qualify a person for the metabolic syndrome as outlined in Table 1. The cut-points were uniformly defined for all components except waist circumference, for which national or regional cut-points can be used. Waist measurement was suggested a useful preliminary screening tool for the metabolic syndrome. Since elevated fasting plasma glucose or drug treatment of elevated glucose were included in the definition, it means that all people with diabetes have this component. Furthermore, since most people with T2D are obese and many have dyslipidaemia and hypertension a majority of them are classified as having the metabolic syndrome. Only blood pressure and plasma glucose cut-points were similar for both sexes, while the other three components (elevated waist circumference, elevated serum triglycerides and reduced HDL cholesterol) had sex-specific cut-points.

Whether the clustering of factors that currently are included in the metabolic syndrome really exists can be best evaluated using epidemiological data and factor analysis. Such an attempt was made using the population-based data of Finnish men.[14] Four factors were identified, one of them included systolic blood pressure, serum HDL-cholesterol and triglycerides, body-mass index and fasting serum insulin, i.e. a cluster of parameters indicating the metabolic syndrome.

Is there a common background for the components of the metabolic syndrome?

In 2005, a joint statement of the American Diabetes Association and the European Association for the Study of Diabetes, 'The metabolic syndrome: Time for a critical appraisal',[15] raised several questions regarding the syndrome. After the 'harmonized' definition of the metabolic syndrome in 2009.[1,3] Reaven in 2011 argued that little had been achieved to establish pathophysiological understanding and clinical utility of the metabolic syndrome despite the vast number of published papers about this syndrome.[12] Nevertheless, there have been various attempts to propose a uniform origin for the clustering of the components of the metabolic syndrome including: (i) genetics, (ii) insulin resistance, (iii) obesity, (iv) lifestyle, (v) sleep disturbances, (vi) inflammation, (vii) foetal and neonatal programming and (viii) disturbed circadian rhythm of body functions, as briefly discussed below.

Genetics

There are hundreds of markers in the genome that are associated with the biological traits of the metabolic syndrome. Genetic susceptibility may exist at various

levels: within adipose tissue, in insulin signalling pathways, and in regulation of individual components of the syndrome. No common genetic trait has, however, been identified for the metabolic syndrome as such. Thus, each component seems to have its own genetic background.[16,17] In the Malmö Preventive Project in Sweden, 17 known genetic variants were studied in a large cohort of individuals without diabetes followed for 23 years. In this study, the development of the metabolic syndrome was defined as the development of at least three components: obesity, dyslipidaemia, hypertension and hyperglycaemia.[18] None of the studied polymorphisms was associated with more than two components of the metabolic syndrome. Since then, several other attempts have reached similar conclusions. Many genetic variants involved in the pathogenesis of the metabolic syndrome are associated especially with glucose metabolism or lipid metabolism, but there is no uniform genetic pathogenesis for the syndrome itself.[19]

Insulin resistance

Reaven stated in his Banting lecture (1988) that resistance to insulin-stimulated glucose uptake and hyperinsulinaemia are involved in the aetiology and clinical course of three related diseases: T2D, hypertension and coronary artery disease.[5] It was suggested that considering the acute effects of insulin on sympathetic nervous activity, transmembranous cation transport, renal sodium reabsorption, cellular proliferation and lipid metabolism, the presence of insulin resistance and/or hyperinsulinaemia may contribute to the genesis of obesity- and T2D-associated hypertension and possibly also promote dyslipidaemia in these disorders.[20,21] However, since identification of insulin resistance is complex, its interpretation challenging and its detection in clinical settings difficult, it is not possible to recommend that insulin resistance be used for routine measurement in clinical practice.[22] The WHO (1998) definition of the metabolic syndrome included fasting serum insulin to be in the top 25th percentile,[7] but it is well-known that fasting serum insulin is a poor indicator of insulin resistance.

Obesity

Obesity, in various forms, is associated with all other components of the metabolic syndrome. Adipose tissue is a major endocrine organ, secreting substances that may play a critical role in the pathogenesis of the metabolic syndrome. Abdominal obesity (usually but not always indicated by large waist) and ectopic fat deposition in the liver, pancreas and skeletal muscle seem particularly deleterious.[23] The IDF definition of the metabolic syndrome (2005) listed a large waist circumference as a requirement for the metabolic syndrome,[8] but this is not included in the 'harmonized definition'. Nevertheless, the prevalence of abdominal obesity in people with the metabolic syndrome is >80%,[24] but the definition of obesity in different ethnic groups and between sexes has been somewhat difficult to define due to differences in body frames.

Lifestyle

All components of the metabolic syndrome are associated with some issues of lifestyle, namely, unhealthy diet, physical inactivity and poor physical fitness. In principle the metabolic syndrome is unlikely to develop without an unhealthy lifestyle even if there are large variations among people with the metabolic syndrome regarding the presence of various unhealthy habits. Thus, it is difficult to define which lifestyle habit is individually most important. It is also difficult to generalize mechanisms of how diet, nutrients and physical activity operate in promoting or preventing the metabolic syndrome. Since people's lifestyles are related to their socio-economic environment, many of the lifestyle habits may have rather complex origins. There is an inverse association between socio-economic status and the metabolic syndrome.[25] On the other hand, it has been shown that relatively simple lifestyle intervention programmes emphasizing a sufficient amount of physical activity and avoiding excess saturated fats, salt and simple sugars are helpful for the people with the metabolic syndrome and can improve all components of the syndrome.[26–29]

Sleep patterns

Meta-analyses suggest that poor sleep duration is a potential risk factor for the metabolic syndrome.[30] Experimental studies support associations between short-term sleep deprivation and physiological changes related to individual metabolic syndrome components such as weight gain, insulin resistance and elevated nocturnal blood pressure. Obstructive sleep apnoea is associated with increased cardiovascular disease.[31] Although it was previously assumed that this was due to its relation with obesity, recent data suggest that sleep apnoea is independently associated with the cardiovascular risk factors that comprise metabolic syndrome, including hypertension, insulin resistance, impaired glucose tolerance and dyslipidaemia.[32] There are multiple mechanistic pathways involved in the interaction between obstructive sleep apnoea, obesity and metabolic derangements.

Chronic inflammation

Several studies on the association between metabolic syndrome and C-reactive protein (CRP) have been reported. Several studies have reported that proinflammatory cytokines, such as interleukin-6, tumour necrosis factor-a and several others, play important roles in the relation between metabolic syndrome and cardiovascular disease.[33] A chronic inflammatory process is known to play an important role in the pathogenesis of atherosclerosis.[34,35] Thus, obesity or metabolic syndrome could influence the development or progression of atherosclerosis and with CRP being involved in this process. Adipokines are considered to be directly linked to pathologies associated with obesity, particularly insulin resistance and the metabolic syndrome. White adipose tissue may be the main site of chronic inflammation in obesity. It is the source of increased circulating levels of inflammatory markers reflecting spill-over from an inflamed tissue. Adipose tissue contributes to the inflammatory pathways through the release of proinflammatory adipokines such as leptin and chemerin and dysregulation of anti-inflammatory adiponectin. Circulating inflammatory biomarkers including CRP, fibrinogen, serum amyloid A, cytokines and chemokines derived from monocytes are also altered and promote inflammation and insulin resistance. It is still unclear to what extent inflammatory markers are directly linked with the metabolic syndrome and, in addition, with cardiovascular disease, and to what extent they are side products of an ongoing pathological process. At the moment their clinical utility is unclear, although CRP is used in various ways in clinical routine, although not to diagnose the metabolic syndrome.

Foetal and neonatal programming

Foetal and neonatal programming can increase the risk for future diseases and are an example of phenotypic plasticity seen throughout nature. For instance, infants born with low birth weight, as a marker of an unfavourable intrauterine environment, are programmed differently and may run an increased risk for multiple diseases, especially cardio-metabolic ones, in adulthood. This was first pointed out in the 1980s by Barker et al. in the UK.[36] Early catch-up growth, that is, adiposity rebound of infants born small, will further increase the risk of metabolic disturbances.[37]

Circadian rhythm

Recently, increasing interest has focused on the involvement of the circadian system, a major regulator of many aspects of metabolism and endocrine function. Effects of the circadian rhythm have been implicated in several chronic diseases, including T2D and cardiovascular disease.[38] While the circadian phenomenon has been known for many body functions, there is now increasing evidence connecting disturbances in circadian rhythm with the key components of the metabolic syndrome: blood pressure, blood lipids, blood glucose and adipose tissue. Moreover, such disturbances have been found to be associated with several comorbidities of the metabolic syndrome. including sleep disturbances, depression, steatohepatitis and cognitive impairment. In a recent publication Zimmet et al.[39] proposed that circadian disruption may be an important underlying aetiological factor for the metabolic syndrome and suggest that it be renamed the 'circadian syndrome'.

Clinical implications of the metabolic syndrome

Cardiovascular risk

Two Finnish studies were the first to evaluate the impact of the metabolic syndrome on cardiovascular disease and mortality using either WHO or ATP III criteria. Lakka et al.,[14] using both criteria, showed that middle-aged men with the metabolic syndrome were at greater risk for coronary heart disease death, cardiovascular death and total mortality than those without (Figure 1). Likewise Isomaa et al.[40] showed a higher cardiovascular disease and total mortality in Finnish and Swedish adults with the metabolic syndrome than those without according to the WHO definition.

These early reports have been cited as proof that the concept of the metabolic syndrome was useful for diagnosis and treatment. Using the US National Health and Nutrition Examination Survey (NHANES) data Malik et al.[41] studied the impact of the metabolic syndrome on coronary heart disease, cardiovascular disease and overall mortality in a representative sample of adults. These endpoints were all significantly higher in people with than in those without the metabolic syndrome. The metabolic syndrome was a better predictor of cardiovascular disease and total mortality than its individual components. The prevalence of the syndrome was 26%. In a previous analysis of the same NHANES data the prevalence increased from 7% among participants aged 20–29 years to 44% and 42% for participants aged 60–69 years and $\geq$70 years, respectively.[42]

In 2005 Ford carried out a meta-analysis to estimate the impact of the ATP III and WHO definitions of the metabolic syndrome on all-cause mortality, cardiovascular disease and T2D as reported in prospective

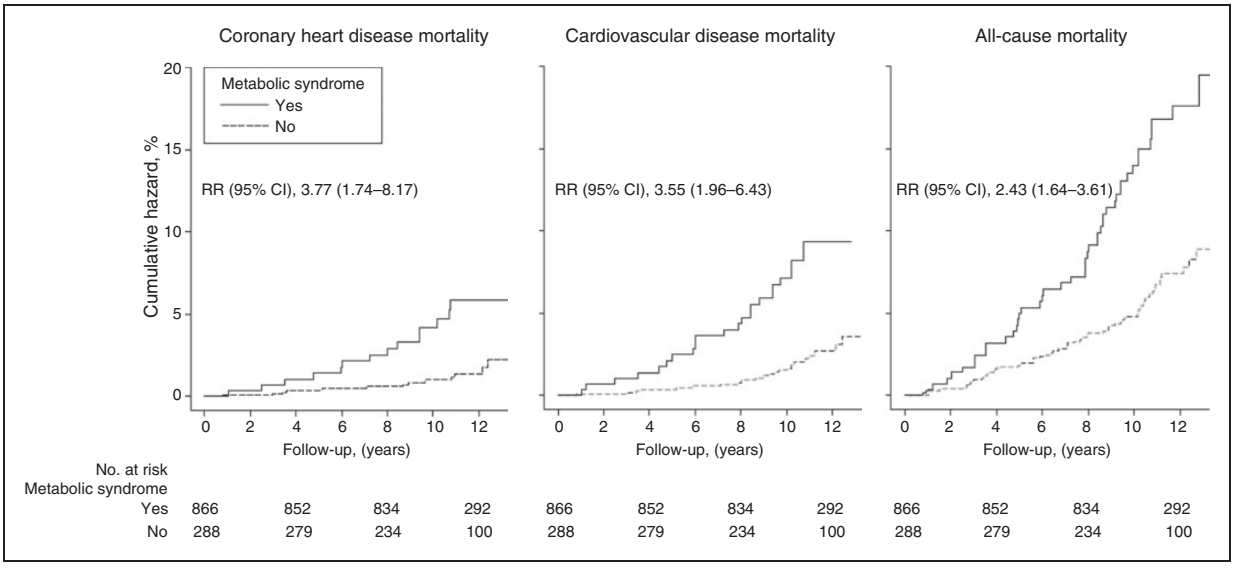

Figure 1. Mortality in Finnish men with and without the metabolic syndrome, aged 42 to 60 years at start of follow-up.
RR: relative risk; CI: confidence interval.
Source: adapted and reproduced with permission from American Medical Association, 2019.[14]

samples of the general population.[43] The relative risks for both all-cause mortality (1.27–1.37) and cardiovascular disease (1.65–1.93) were statistically significant and similar for both definitions of the syndrome. He also estimated that the population-attributable risk (PAR) fraction for the metabolic syndrome was 6–7% for all-cause mortality and 12–17% for cardiovascular disease. A European collaborative study included 11 cohort studies on adults without diabetes aged from 30 to 89 years with a median follow-up of 8.8 years.[44] The metabolic syndrome was diagnosed by a modified WHO definition: hyperinsulinaemia and two or more of obesity, hypertension, dyslipidaemia or impaired glucose regulation. The age-standardized prevalence of the metabolic syndrome was 16% in men and 14% in women. The adjusted (age, serum cholesterol and smoking) hazard ratios for all-cause and cardiovascular mortality in persons with compared with those without the metabolic syndrome were 1.44 and 2.26 in men and 1.38 and 2.78 in women respectively.

Attempts have been made to compare the predictive ability of the metabolic syndrome for cardiovascular disease with the Framingham Risk Score (FRS).[45] The metabolic syndrome did not improve the risk prediction beyond that achieved by the FRS in some studies[46,47] while one study reported that the metabolic syndrome was a significant predictor of cardiovascular disease even after FRS adjustment.[48] In the INTERHEART study ($N = 26{,}903$) involving 52 countries the metabolic syndrome was associated with 2.2-to 2.7-fold increased risk of myocardial infarction. The associations were directionally similar across all regions and ethnic groups.[49] The authors emphasized that dichotomizing risk factors that are continuous variables underestimates risk and decreases the magnitude of the association.

The presence of the metabolic syndrome, in people with or without diabetes, also increases risk for ischaemic stroke or transient ischaemic attacks.[50] A meta-analysis suggested that women with the metabolic syndrome were more sensitive (relative risk (RR) 1.83) than men (RR 1.47), and that people with the metabolic syndrome had a significantly higher risk of ischaemic (RR 2.12) than of haemorrhagic stroke (RR 1.48).[51]

T2D risk

Early studies assessed the risk of developing T2D among people with the metabolic syndrome defined according to the National Cholesterol Education Program or WHO criteria.[52–55] The estimated RR was 3–6, that is, higher than that for cardiovascular disease. In the meta-analysis by Ford.[43] the PAR fraction for the metabolic syndrome to develop T2D was 30–52%.

Dementia risk

A recent meta-analysis included reports from 12 studies ($N = 6865$) aiming at quantifying the risk of progression from mild cognitive impairment (MCI) to frank dementia in people with and without T2D, and with and without the metabolic syndrome.[56] The overall unadjusted pooled odds ratio for the progression of MCI to

dementia in people with T2D/metabolic syndrome was 1.67 and the pooled odds ratio for progression in T2D + MCI 1.53 while it was 2.95 in people with the metabolic syndrome + MCI. Thus, T2D and the metabolic syndrome were both associated with an increased incidence of dementia when co-existing with MCI.

Managing the metabolic syndrome

The importance of a healthy lifestyle for the prevention of pre-diabetes and T2D is well established and the evidence is stronger than that for primary prevention of cardiovascular disease based on lifestyle modifications alone. The most important studies to show benefits for prevention of T2D are the Da Qing Study in China,[57,58] the Malmö Feasibility Study in Sweden,[59] the Diabetes Prevention Study in Finland,[60] and the Diabetes Prevention Program in the USA.[61] The most important lifestyle study for primary prevention of cardiovascular disease is the Spanish Prevención con Dieta Mediterránea (PREDIMED) study.[62] These studies will be briefly reviewed, as well as meta-analyses that apply. In addition some new perspective will be introduced together with some remarks regarding the balance between individual approaches and structural (non-individualized) strategies to counteract the development of cardiometabolic disease and T2D in individuals and populations. More recently the molecular mechanisms behind the benefits of exercise training have been described, strengthening the importance of this mode of intervention in patients with the metabolic syndrome or T2D.[63]

The Da Qing study

This cluster-randomized trial, which started in 1986, engaged 33 clinics in Da Qing, China. They were randomly assigned to either serve as a control clinic or to provide one of three interventions, diet, exercise or diet plus exercise, during six years. The trial recruited 577 adults with impaired glucose tolerance (IGT).[57] After the six active study years the participants were followed for up to 30 years to assess the effects of intervention on the incidence of T2D, cardiovascular events, a composite of microvascular complications, cardiovascular death, all-cause mortality and life expectancy. Of the 577 participants, 438 were assigned to one of the intervention groups and 138 to the control group. A total of 540 (94%) of the participants were assessed after 30 years. When compared with the control group participants in the combined intervention group had a median delay in the onset of T2D of 3.96 years (95% confidence interval (CI): 1.25–6.67; $p = 0.0042$), fewer cardiovascular events (hazard ratio 0.74), a lower incidence of microvascular complications (hazard ratio 0.65) and fewer cardiovascular (hazard ratio 0.67) and all-cause deaths (hazard ratio 0.74). Their average increase in life expectancy was 1.44 years.[58] The authors concluded that this lifestyle intervention in people with IGT delayed the onset of T2D and reduced the incidence of cardiovascular events. An important lesson is that an initial lifestyle programme should be sustained over a long period (Figure 2).

The Malmö feasibility study

From a screening programme of 6956 men (47–49 years old) from Malmö, Sweden, 41 with early-stage T2D and 181 with IGT detected by means of an oral glucose tolerance test were selected for a prospective, non-randomized study. The objective was to test the feasibility of a long-term intervention with an emphasis on lifestyle changes including dietary treatment and/or increase of physical activity or training with annual check-ups.[59] The study was completed by 90% of subjects. Body weight was reduced by 2.3–3.7% among participants while it increased by 0.5–1.7% in non-intervened men with IGT and in normal control subjects ($p < 0.0001$). Glucose tolerance was normalized in >50% of subjects with IGT and blood pressure, lipids and hyperinsulinaemia were reduced. The improvement in glucose tolerance was correlated to weight reduction and increased physical fitness. The authors concluded that the treatment was safe and that mortality was 33% lower than in the background cohort.[59]

The Diabetes Prevention Study

In Finland, 522 middle-aged, overweight persons (women 67%; mean age 55 years; mean BMI 31 kg/m^2) with IGT were randomized to either an intervention or a control group.[60] Each subject in the intervention group received individualized counselling aimed at reducing weight, diminishing the total intake of fat and reducing saturated fat, increasing the intake of fibre and promoting physical activity. The mean duration of follow-up was 3.2 years. The cumulative incidence of T2D after four years was 11% (95% CI 6–15) in the intervention group and 23% (95% CI 17–29) in the control group. During the trial, the risk to develop T2D was reduced by 58% ($p < 0.001$) in the intervention group. This reduction was directly associated with changes in lifestyle.

The Diabetes Prevention Program

In the USA, a total of 3234 persons free from T2D (68% women; mean age 51 years; mean BMI 34.0 kg/m^2) but with elevated fasting and post-load plasma glucose concentrations were randomized to placebo, metformin

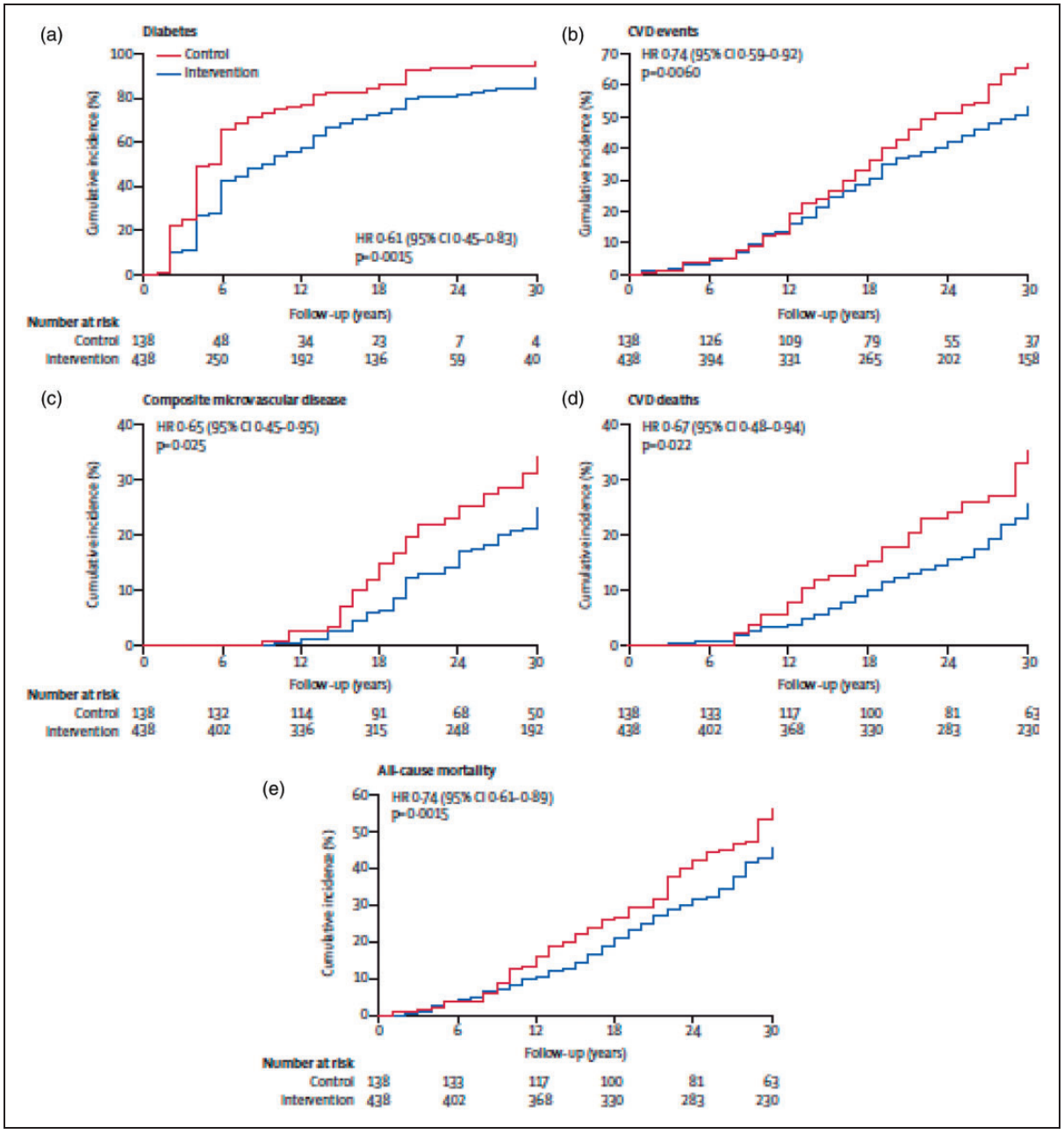

Figure 2. Development of diabetes (a), cardiovascular events (b), microvascular events (c), cardiovascular mortality (d) and total mortality (e) during 30 years of follow-up in the Da Qing trial.
Both mortality types decreased by lifestyle intervention in patients with impaired glucose tolerance at baseline. Noteworthy is the rather long time it takes until the benefit in mortality starts to develop.
HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease.
Source: reproduced with permission from Elsevier, 2019.[58]

(850 mg b.i.d.), or a lifestyle-modification programme targeting a weight loss ≥7% and ≥150 min of weekly physical activity.[61] After an average follow-up of 2.8 years the T2D incidence was 11.0, 7.8, and 4.8/100 person-years in the placebo, metformin and lifestyle groups, respectively. Accordingly, the lifestyle intervention was the most efficient, reducing the incidence by 58% (95% CI 48–66) compared with 31% with metformin. During a period of three years this translates to a number needed to treat of 6.9 to prevent one case of T2D with lifestyle-intervention compared with 13.9 for metformin.[61]

The PREDIMED study

This primary preventive study randomized 7447 middle-aged subjects free from cardiovascular disease to either an intensified Mediterranean diet, with extra olive oil or extra nuts, or to a standard diet.[62] After a median follow-up of 4.8 years the risk of incident cardiovascular events was significantly reduced in the intervention group without any difference between participants given extra olive oil or extra nuts. In the intention-to-treat analysis including all the participants and adjusting for baseline characteristics and propensity scores, the hazard ratio was 0.69 (95% CI 0.53–0.91) for a Mediterranean diet with extra-virgin olive oil and 0.72 (95% CI 0.54– 0.95) for a Mediterranean diet with nuts compared with the standard diet.

Meta-analyses report evidence for interventions

A number of systematic reviews and meta-analyses, built on different designs and time frames, support lifestyle interventions based on dietary changes, weight control and physical activity for prevention of T2D.[64–73] In one of the most recent Haw et al.[71] pooled 43 studies (participants 49,029; mean age 57.3 years; women 52%). Nineteen of these studies tested medications, 19 lifestyle modification, and five lifestyle modification in combination with medications. At the end of the active intervention (range 0.5–6.3 years) lifestyle modification was associated with a RR reduction for T2D of 39% (RR 0.6; 95% CI 0.54–0.68) and medications with an RR reduction of 36% (RR 0.64; 95% CI 0.54–0.76). The authors concluded that in adults at risk for T2D, lifestyle modification and medications (weight loss and insulin-sensitizing agents) successfully reduced the future incidence. The effects of medication were short lived while the lifestyle modification interventions were sustained for several years.[71]

This message is further strengthened by data from an intervention study aimed at weight loss and reversal of early T2D in overweight/obese subjects, the Diabetes Remission Clinical Trial.[74] Furthermore, according to recent findings in the Whitehall II observational study of civil servants in London, the reversal of pre-diabetes was also associated with a lowered cardiovascular risk during long-term follow-up.[75]

However, critical voices have been raised arguing that the currently available screening methods for dysglycaemia, based on fasting plasma glucose, post-challenge glucose, or HbA_{1c}, are imprecise and that the intervention offered does not reach the right people, with questionable long-term effects.[76] Instead more 'upstream' (societal) interventions are called for such as taxation and healthy food programmes as proposed by the WHO.[77]

New perspectives on diabetes prevention

Low birth weight

In a life course perspective it is very relevant to consider the early life predictors and opportunities for prevention of cardiometabolic disease and T2D.[78] Low birth weight and impaired foetal growth, often resulting in small-for-gestational-age babies, have been linked to increased risk of hypertension, cardiovascular disease and T2D in adult life. Thus, preventive maternal and child health care starting already in the pre- and post-conceptional periods could have long term beneficial consequences. A healthy lifestyle and appropriate dietary intake of vitamins, for example, folic acid, and nutrients in young women may improve the chances for a healthy embryonal and foetal development.[79] This should be followed by avoidance of smoking and alcohol consumption during pregnancy, and encouragement of breast feeding in the post-natal period. The weight trajectories of young children have been studied and linked to the development of cardiometabolic disease. This is especially relevant for the so called mis-match concept[80] when small-for-gestational-age babies grow too rapidly in early post-natal life ('catch-up growth') that could eventually over-stretch the biological capacities of inner organs, with resulting beta-cell impairment in insulin secretion in adult life if the subjects becomes obese and sedentary, causing insulin resistance, at elevated risk for T2D. This means that an appropriate diet and regular physical activity in children and adolescents could positively contribute to a normal bodily development (weight trajectories) and decrease the risk of cardiometabolic problems in adult life.

Gastrointestinal microbiota

Another emerging field of interest is the interaction between dietary intake, genetic set-up and the gastrointestinal microbiota patterns for development of T2D.[81] Adult subjects with obesity or features of the metabolic syndrome, for example, hypertension, have been shown to have less bacterial diversity in the gastrointestinal tract with a relative lack of healthy and predominance of less healthy bacterial strains.[82,83] As microbiota patterns are first programmed at birth and in early life, this opens another opportunity for promoting healthy diet in young people, including breastfeeding in the new born.

Subjects at increased genetic risk benefit from healthy lifestyle

The rapidly developing knowledge of genetic factors influencing cardiometabolic disease risk has provided new insights in the genetic architecture behind T2D,

both for more common and less common (rare) variants based on genome-wide association study and exome sequencing.[84] The same is true for hypertension, obesity and coronary heart disease. This should, however, not distract the interest in lifestyle improvements as part of prevention. In fact, recent studies have shown that subjects at high genetic risk can modify their risk by practising a healthy lifestyle.[85] Therefore, genetic information of high risk should encourage healthy lifestyle habits even more and not lead to fatalism or even depression.

Need for both individual and structural interventions

One critical view on the individualization of preventive measures for patients at risk is that this has not always been well adapted for people with less education, adverse social background or other detrimental factors that could distract from finding time and motivation for improving their individual lifestyle. Therefore more structural and societal changes are needed to facilitate primary prevention of cardiovascular disease and T2D.[86] Examples are taxation, food labelling, city planning, social reforms, health literacy, et cetera. As the epidemics of obesity, malnutrition and environmental problems act synergistically for a so called global *syndemic*,[87] only social reforms and political decisions can be effective at a population and public health level. This should not distract the attention of physicians, nurses and health counselling advisors from their individual patients, but inform them about the importance and primacy of structural perspectives. This also applies to families at high cardiometabolic and T2D risk where early screening and prevention of risk could be offered,[88] being of special relevance for the prevention of T2D.[89]

The consultation as the basis for successful prevention

All our evidence-based knowledge will count for nothing if we cannot build trust with and reach the patient in need of preventive measures for cardiometabolic health. It is of great importance to find the fine balance between giving alarming information about risk on one side and showing a hopeful and reassuring attitude on the other.[90] In this perspective, one should remember the words of Sir William Osler (1849–1919): 'Ask not what disease the person has, but rather what person the disease has'.

The first step in the consultation is to get to know each other and build trust and a working alliance. Knowledge transfer comes thereafter and should not be unidirectional. The physician, nurse or health counselling staff are the experts on the medical aspects, but the patient is the expert on his/her own personal history, bodily experiences, symptoms and worries. One starting point could be to ask the patient what he or she is afraid of in relation to cardiometabolic health, often mirrored by family history and early onset of such disorders in close relatives. The knowledge transfer of how the body works and how risk factors act should be accompanied by continuous trust building and motivation. In complex situations with a mix of biological risk factors, adverse social conditions and unhealthy lifestyle, everything cannot be changed at once. It is better to aim for small steps that are lasting than large, unsustainable steps with relapses of unhealthy behaviours.[91] Often a supportive spouse or family network is the success factor to recognize and build upon. Feedback and encouragement is standard. Even if the physician has developed a plan (agenda) for the lifestyle improvements and risk factor control there will be relapses, disappointments and need of a new start. Some individuals are even in denial or suspicious of the lifestyle advice provided, they may have their own odd ideas about, for example, dietary requirements or the imagined perils of physical activity. In such cases one should, if the patient prefers, encourage a second opinion via consultation with other experts, hopefully giving the same health message. In other cases there is a fatalistic attitude toward health issues. This is a coping mechanism in people with a low trust in the society, the medical profession or in those who are victims of oppressing social circumstances with a very limited degree of freedom to make rational choices. The first step should be to apply an empathetic and listening attitude. After further visits and trust building, the patient may look differently at the existing health issues.

Sometimes it is easier to add a healthy habit than to immediately get rid of an unhealthy one, as shown in a study on cardiac rehabilitation.[92] Therefore the professional could recommend the addition of some healthy diet components or daily walks, instead of banning bad habits in the first place. With time the patient may realize that he or she feels better and will be more willing to abandon the bad habits.

A sensitive question is whether financial incentives can be used to promote healthy lifestyle in at risk patients. This has been tried in so called quit-and-win campaigns for smoking cessation, with varying results,[93] even including paying a sum to high-risk patients to quit their tobacco habit.[94] The counterargument is that this is not a long-lasting effect and ethically doubtful. However, there are unexplored models that could be of some importance. We know for example that childhood obesity tracks in families and that many obese children, but not all, will end up as obese adolescents and young adults with an increased risk for

the metabolic syndrome. A possibility would be a randomized trial to evaluate paying parents a fixed sum to make sure their obese 5–7-year-old children are attending sports activities or classes to increase physical activity three times a week. If this could last for two to three years, the incentive could then stop in the hope that such healthy habits formed during early years could be lasting.

Concluding remarks

A cluster of metabolic factors exists that were harmonized into a definition of the metabolic syndrome in 2009. The metabolic syndrome predicts cardiovascular disease and T2D. The risk associated with the metabolic syndrome does not exceed its components, whereof elevated blood pressure is the most frequent. A successful management should, however, address all factors involved. The management is always based on healthy lifestyle choices but has frequently to be supported by pharmacological treatment, especially by means of blood pressure lowering drugs. The metabolic syndrome is a useful example of the importance of multiple targets for preventive interventions. A person with the metabolic syndrome will always be afflicted with its components, which is the reason that management has to be sustained over a very long time. Drug treatment for the components of the syndrome has to be prescribed on an individual basis, and frail elderly people should not be over-treated.

Author contribution

PN, JT and LR all contributed to the conception and design of the review and each of them provided a first draft of different parts of the manuscript. This was put together by LR and subsequently critically revised by PN and JT. All authors gave their approval of the final manuscript and are accountable for all aspects of the final review.

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