Review paper

Prevalence and factors related to the metabolically obese normal-weight (MONW) phenotype: a review

Częstość występowania i czynniki powiązane z fenotypem metabolicznej otyłości z prawidłową masą ciała (MONW): przegląd piśmiennictwa

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Słowa kluczowe: dieta, aktywność fizyczna, rozpowszechnienie, czynniki genetyczne, otyłość metaboliczna z prawidłową masą ciała.

Abstract

The aim of this review was to assess the prevalence and factors related to the metabolic obesity with normal weight (MONW) phenotype. Studies published in English up to December 2021 in the PubMed, Science Direct and Google Scholar databases were searched. The prevalence of MONW is estimated to range from 1.0% to 28.6%, depending on the age of the study participants and the definition of MONW used in the studies. Difficulties in determining the genetic causes of MONW result primarily from the lack of a uniform definition and from the complexity of the disorder. Each component of MONW may be determined by different genes. A person's lifestyle, in particular their diet, seems to be a significant factor in the development of MONW. Studies have so far been unable to determine the optimal type and duration of dietary intervention needed to improve the metabolic parameters in individuals with MONW.

Streszczenie

Celem pracy była ocena częstości występowania i czynników związanych z fenotypem metabolicznej otyłości z prawidłową masy ciała (MONW). Dokonano przeglądu prac dotyczących rozpowszechnienia MONW, opublikowanych w języku angielskim do grudnia 2021 r. w bazach PubMed, Science Direct i Google Scholar. Występowanie MONW w różnych populacjach jest szacowane na 1–28,6%, w zależności od wieku uczestników i definicji fenotypu przyjętej przez autorów badania. Trudności związane z określeniem uwarunkowań genetycznych MONW wynikają przede wszystkim z braku jednolitej definicji oraz ze złożoności zespołu. Każdy komponent MONW może być determinowany przez różne geny. Wydaje się, że istotną rolę w rozwoju tego fenotypu odgrywa styl życia, w szczególności sposób żywienia. Dotąd nie wyjaśniono jednak, jaki rodzaj i czas trwania interwencji dietetycznej byłby najbardziej skuteczny w poprawie parametrów metabolicznych u osób z MONW.

Introduction

Metabolic disorders – impaired glucose tolerance, dyslipidaemia and high blood pressure (BP) – are typical comorbidities of obesity. However, these disorders have also been reported to occur to varying degrees in normal-weight patients (i.e. patients with a normal body mass index (BMI)) among different populations. Numerous studies have confirmed that patients with metabolic disorders, despite having a normal BMI, are at a higher risk of heart diseases, including myocardial infarction, heart failure and cardiovascular diseases (CVD) [1–4], hypertension [3], type 2 diabetes [5, 6], non-alcoholic fatty liver disease [7], many tumours [8], chronic kidney disease [9] and mortality [1, 10, 11]. However, due to their having a normal weight, such patients are usually unaware of the risks and do not undergo any prophylactic programmes or routine check-ups.

The aim of this review was to assess the prevalence of metabolic obesity with normal weight (MONW) and to analyse the factors related to the occurrence of the phenotype, including both genetic factors and lifestyle.

Material and methods

Definition of MONW

At the time of writing this paper, there is no uniform, standardised, widely accepted definition

of metabolic disorders in normal-weight individuals. The term *'metabolically obese normal-weight'* was introduced by Ruderman *et al*. [12], and many other terms also appeared in the subject literature over the years, such as 'metabolically unhealthy non-obese' ('MUNO [13] or MUNHO [14]) and 'metabolically unhealthy normal-weight' (MUNW [15, 16] or MUHNW [17]. De Lorenzo *et al*. described four phenotypes of obesity according to the composition and distribution of adipose tissue: 'normal-weight obese' (NWO), 'metabolically obese normal-weight' (MONW), 'metabolically healthy obese' (MHO) and 'metabolically unhealthy obese' (MUO) [18]. Thus, according to the classification proposed by de Lorenzo *et al*., normal weight obese (NWO) and metabolically obese normal-weight (MONW) are two separate phenotypes. The NWO phenotype should be treated as 'fat mass disease' and the MONW phenotype as 'sick fat disease'. In this review, studies were taken into account that classify their participants as having a normal weight for a given population and at least one metabolic disorder in the form of impaired glucose tolerance, dyslipidaemia or high BP.

Literature search strategy

We searched for studies on the prevalence of MONW published in English up to December 2021 in the PubMed, Science Direct and Google Scholar databases, using the following terms: 'metabolically obese but normal weight' or 'metabolically unhealthy normal weight' and 'prevalence', 'genome-wide association studies (GWAS)', 'genetic variants', 'lifestyle', 'smoking', 'diet', 'dietary patterns', 'nutrients', 'caloric restriction', 'intermittent fasting', 'energy expenditure', 'physical activity', 'sitting time', and 'sleep'. The reference lists of the studies extracted from the primary electronic search were also used to identify additional relevant articles. The prevalence of MONW was only analysed based on those studies with a determinable percentage of subjects having MONW compared to the total population and normal-weight subjects.

Prevalence of MONW and transitions between phenotypes

Adults with MONW are estimated to make up 1.0–28.6% of different populations, depending on the age of the study participants and the definition used by the authors (Tables 1–3) [19–48]. A higher prevalence of MONW is usually observed in men than in women [22], as well as in older age groups than in younger ones [22, 39] and in ethnic groups in which visceral adiposity is high despite a low overall BMI [17, 16]. Wildman *et al*. reported a MONW prevalence of 30.1%

Table 1. Prevalence of MONW in adults (≥ 1 metabolic abnormalities)

Author	Studied population and age of the participants	Definition of MONW used by the authors	Prevalence: 1) within the population (%) 2) percentage of subjects with normal-weight
Diniz *et al*. [19]	Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) A cross-sectional study among 14,545 participants aged 35–74 years	BMI = 18.5–24.9 kg/m^2 MONW was classified according to four commonly used criteria: those used in the National Health and Nutrition Examination Survey (NHANES), NCEP, IDF and comorbidity criteria (presence of arterial hypertension, diabetes mellitus or dyslipidaemia); individuals were considered metabolically unhealthy if classified as such by any of the four criteria	1) 18.8% 2) 51.4%
Xia *et al*. [20]	Shanxi Province, China, 3015 adults aged 18–79 years	BMI = 18.5–23.9 kg/m^2 Presence of one or more components according to NCEP ATP III (excluding WC)	1) 28.6% 2) 51.0%
Kunzova *et al*. [21]	Data from the CoLaus (5,745 participants in Lausanne, Switzerland) and the Kardiovize Brno 2030 with 1,852 participants from Brno, Czech Republic, cohorts aged 25–64 years	BMI from ≥ 18.5 to < 25 kg/m^2 Metabolically unhealthy individuals were defined as presenting at least one of the IDF criteria (excluding WC)	1) 4.9% and 10.3% 2) 10.1% and 21.5% in Czech and Swiss populations, respectively

BMI – body mass index, WC – waist circumference, NCEP ATP – National Cholesterol Education Programme Adult Treatment Panel, IDF – International Diabetes Federation, NHANES – the National Health and Nutrition Examination Survey.

Table 2. Prevalence of MONW in adults (≥ 2 metabolic abnormalities)

Author	Studied population and age of the participants	Definition of MONW used by the authors	Prevalence: 1) within the population (%) 2) percentage of subjects with normal-weight
Wildman *et al.* [22]	5440 US adults (NHANES 1999-2004) aged ≥ 20 years	BMI < 25.0 kg/m^2 ≥ 2 cardiometabolic abnormalities: HOMA-IR ≥ 2.7, TG ≥ 1.7 mmol/l or use of lipid lowering drugs, HDL-C ≥ 1.0/1.3 mmol/l for men/ women, LDL-C ≥ 2.6 mmol/l, hs-CRP ≥ 3.0 mg/l	1) 8.1% 2) 23.5%
Lopez-Garcia *et al.* [23]	A cross-sectional study conducted in 2008–2010 among 11,520 Spanish adults, a group representative of a population aged ≥ 18 years	BMI < 25 kg/m^2 ≥ 2 cardiometabolic abnormalities out of the following six: elevated BP (SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg and/or antihypertensive medication use); TG (≥ 150 mg/dl); low HDL-C (< 40 mg/dl for men and < 50 mg/dl for women and/ or lipid-lowering medication use); elevated glucose (≥ 100 mg/dl and/or antidiabetic medication use); HOMA-IR (> 4.05, the 90th percentile); hsCRP (> 0.74 mg/dl, the 90th percentile)	1) 6.4% 2) 16.8%
Buscemi *et al.* [24]	1019 participants from the cohort of the ABCD_2 (Alimentazione, Benessere Cardiovascolare e Diabete) study, Palermo (Sicily), Italy, aged 18–90 years	BMI < 24.9 kg/m^2 ≥ 2 of the following conditions: prediabetes/ type 2 diabetes, hypertension, hypertriglyceridaemia or low HDL cholesterol (according to the IDF guidelines), and hypercholesterolaemia (defined as values > 200 mg/dl or use of a cholesterol-lowering medication)	1) 9.52% 2) 36.7%
Gujral *et al.* [25]	2622 white, 1893 African American, 1496 Hispanic and 803 Chinese American participants from the Multi-Ethnic Study of Atherosclerosis (MESA), and 803 South Asian participants from the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study aged 45–84 years	BMI = 18.5–24.9 kg/m^2 was considered normal for African American and Hispanic participants BMI =18.5–22.9 kg/m2 was considered normal for South Asian and Chinese American participants ≥ 2 components of MetS according to NCEP ATP III (excluding WC)	1) 7.46% 2) 29.13%
Rotar *et al.* [26]	Cross-sectional multicentre population-based study entitled 'Epidemiology of cardiovascular diseases and its risk factors in some regions of the Russian Federation' (ESSE-RF), with a random sampling of 21,121 subjects (25–65 years)	BMI < 25.0 kg/m^2 Underweight individuals (BMI ≤ 18.5) were excluded from the analysis ≥ 2 markers according to Oliveros *et al.* [27]	1) 5.66% 2) 18.09%
Hajian-Tilaki and Heidari [28]	A random sample of the adult population of north Iran, 986 subjects aged 20–70 years	BMI > 18.5 and < 25 kg/m^2 Presence of ≥ 2 non-obese components of the metabolic syndrome based on the NCEP ATP III criteria	1) 17.2% 2) 52.5%
Rahmanian *et al.* [29]	Jahrom Health Study (urban adult population in Jahrom, Iran), 891 subjects aged 30–91 years	BMI < 25 kg/m^2 Presence of 2 or more cardio-metabolic abnormalities, as defined by NCEP ATP III in 2002	1) 14.6% 2) 37.5%

Table 2. Cont.

Author	Studied population and age of the participants	Definition of MONW used by the authors	Prevalence: 1) within the population (%) 2) percentage of subjects with normal-weight
Izumida *et al.* [30]	10,824 participants, part of the Jichi Medical School (JMS) Cohort Study, Japan; mean ± SD age 55.3 ±11.5 years	BMI = 18.5–24.9 kg/m^2 No fewer than two of the following criteria (excluding WC): systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg or treatment for hypertension, elevated TG (≥ 150 mg/dl), low HDL-C (men, < 40 mg/dl; women, < 50 mg/dl), high fasting glucose (≥ 100 mg/dl, with a fasting duration of at least 3 h), high casual glucose (≥ 140 mg/dl for less than 1 h since last meal, ≥ 120 mg/dl for 1 to 2 h, and ≥ 110 mg/dl for 2 to 3 h), or treatment for diabetes mellitus	1) 25.7% 2) 36.0%
Samouda *et al.* [31]	European Health Examination Survey conducted in Luxembourg between 2013 and 2015, with 1,422 individuals aged 25–64 years	BMI scores of 18.5–25 kg/m^2 MONW defined as having two or more cardiometabolic abnormalities according to the IDF guidelines (low HDL cholesterol, high blood pressure, high fasting glucose or triglycerides, and/or previously diagnosed hypertension or diabetes), but the definition did not include treatment for diabetes, lipids or hypertension	1) 7.7% 2) 18.3%
Mirmirian *et al.* [32]	The participants were selected from Tehran Lipid and Glucose Study; 1114 adults aged ≥ 19 years	BMI = 18.5 to < 25 kg/m^2 An unhealthy phenotype was defined as having more than one metabolic abnormality of the IDF criteria	1) 13.6% 2) 22.3%
Zheng *et al.* [33]	37,815 individuals recruited from the database of the Zhejiang Metabolic Syndrome Cohort in the Zhejiang Province in south-eastern China aged ≥ 20 years	BMI = 18.5–23.9 kg/m^2 At least two metabolically abnormal traits according to the metabolic syndrome criteria from the IDF guidelines	1) 16.1% 2) 34.1%
Fan *et al.* [34]	China North-West Natural Population Cohort: Ningxia Project (CNC-NX); 15,820 adults aged 35–74 years	BMI = 18.5–23.9 kg/m^2 ≥ 2 cardiometabolic risk factors according to NCEP ATP III	1) 12.3% 2) 35.9%
Wang *et al.* [35]	13,525 Uyghur, Kazakh and Han participants in the Kashi, Yili and Shihezi areas in Xinjiang, China; age ≥ 18 years, mean age 45.0 ±14.6 years	BMI = 18.5-23.9 kg/m^2 > 1 metabolic abnormalities according to the NCEP ATP III definition, excluding WC	1) 15.5% 2) 30.1%
Robson *et al.* [36]	3018 participants of the Whitehall II study aged 35–55 years	BMI < 25 kg/m^2 ≥ 2 of the following five cardiometabolic risk factors: BP ≥ 130/85 mm Hg or use of hypertension medication, HDL-C < 1.03 mmol/l for men and < 1.29 mmol/l for women, TG ≥ 1.7 mmol/l, fasting plasma glucose ≥ 5.6 mmol/l or use of diabetes medication, HOMA-IR > 5.1 (the 90th percentile)	1) 5.40% 2) 13.78%

BMI – body mass index, WC – waist circumference, NCEP ATP – National Cholesterol Education Programme Adult Treatment Panel, IDF – International Diabetes Federation, MetS – metabolic syndrome, TG – triglycerides, BP – blood pressure, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, HOMA-IR, homeostasis model assessment of insulin resistance, hsCRP – high-sensitivity C-reactive protein.

Table 3. Prevalence of MONW in adults (≥ 3 metabolic abnormalities)

Author	Studied population and age of the participants	Definition of MONW used by the authors	Prevalence: 1) within the population (%) 2) percentage of subjects with normal weight
Lee *et al.* [37]	5267 adult participants from the 3rd Korean National Health and Nutrition Examination Survey aged ≥ 20 years	BMI < 25 kg/m^2 ≥ 3 abnormal metabolic components: WC of ≥ 90 cm for men and ≥ 85 cm for women; other MetS components: in accordance with NCEP ATP III	1) 8.7% 2) 12.7%
Pajunen *et al.* [38]	Finnish Type 2 Diabetes (FIN-D2D) survey of 2,849 individuals aged 45–74 years	BMI < 25 kg/m^2 Definition of MetS according to the IDF guidelines	1) 7.2% 2) 22.4%
Bradshaw *et al.* [39]	14,663 subjects from the ARIC cohort at first visit, the Atherosclerosis Risk in Communities (ARIC) study – a prospective cohort in four US communities, including men and women aged 45–64 years	BMI < 25 kg/m^2 Definition of MetS according to the NCEP ATP-III guidelines	1) 3.02% 2) 9.2%
Eckel *et al.* [40]	2027 participants from the European Prospective Investigation Into Cancer and Nutrition Potsdam, most aged 35–64 years	BMI < 25 kg/m^2 MetS was defined based on the NCEP ATP III definition, modified by replacing fasting glucose with HbA1c, because fasting samples were not available for most participants	1) 5.7% 2) 12.4%
Suliga *et al.* [41]	Polish-Norwegian Study (PONS) project, Poland, with 12,784 adults aged 37–66 years	BMI = 18.5–24.9 kg/m^2 Definition of MetS according to the IDF guidelines	1) 4.7% 2) 17.3%
Goday *et al.* [42]	Ibermutuamur CArdiovascular RIsk Assessment (ICARIA) study, Spain, aged 16–74 years	BMI = 18.5–24.99 kg/m^2 Definition of MetS according to NCEP ATP III	1) 1.0% 2) 2.2%
Zhang et al. [43]	Chinese Beijing urban population with a total of 22,376 subjects aged 18–85 years	BMI < 25 kg/m^2 MetS was diagnosed according to modified criteria of the IDF and the WHO Asia-Pacific Region guidelines	1) 4.33% 2) 8.15%
Fernández-Verdejo *et al.* [44]	National Health Survey of Chile 2016–2017; 2287 subjects, aged 18–65 years	BMI = from 18.5 to < 25 kg/m^2 Harmonised definition of MetS according to the IDF criteria, but taking into account a WC cutoff specific for the Chilean population	1) 1.6% 2) 7.3%
Ojwang *et al.* [45]	711 adults from the South African arm of the Prospective Urban and Rural Epidemiology study	BMI < 25 kg/m^2 Definition of MetS according to the IDF guidelines	1) 11.1% 2) 18.6%
Zhu *et al.* [46]	2121 adult Asian Americans from the NHANES 2011–2016 database, mean age of 44.18 ±0.69 years	BMI < 23.0 kg/m^2 To define MetS, they used the 2005 definition from the IDF 2006 [47]	1) 5.23% in men 1) 18.61% in women
Zoghi *et al.* [48]	3917 participants of Bandare-Kong Non-Communicable Diseases (BKNCD) Cohort Study, as part of the Prospective Epidemiological Research Studies in Iran (Persian); 3917 participants with the mean age of 48.29 ±9.39 years (35–70 years)	BMI < 25 kg/m^2 The NCEP-ATP III criteria for MetS, along with cutoffs for WC replaced by ≥ 95 cm in both men and women, was used as the Iranian-specific criteria	1) 6.36% 2) 17.34%

BMI – body mass index, WC – waist circumference, NCEP ATP – National Cholesterol Education Programme Adult Treatment Panel, IDF – International Diabetes Federation, MetS – metabolic syndrome, HbA_{1c} – glycosylated haemoglobin.

in men and 21.2% in women [22]. Samouda *et al.* concluded that MONW occurred in men with a four times greater likelihood than in women [31]. A higher prevalence of MONW in women than in men was noted among Chinese Beijing urban subjects [43] and in Asian Americans [46]. Likewise, a study conducted in Finland observed MONW in 23.8% of women and 20.4% of men aged 45–74 years [38].

A study conducted among five ethnic groups from the US showed that the highest prevalence of metabolic disorders in normal-weight subjects occurred among South Asians (43.6%), followed by Hispanics (38.5%), Chinese Americans (32.2%) and African Americans (31.1%), while the lowest rate occurred in Caucasians (21.0%) [25]. The most common combinations of risk factors were a high BP and low high-density lipoprotein cholecterol (HDL-C) concentration in Caucasians and a high glucose concentration and low HDL-C concentration in other ethnic groups. Zhu *et al.* [46] found that for individuals with a BMI > 23 kg/m^2, Asian Americans had a higher predicted risk of metabolic syndrome (MetS) than non-Hispanic White counterparts of the same BMI level.

Research shows that metabolic health is a dynamic state that changes over long-term observations across all BMI categories, with most changes progressing to unhealthy phenotypes. A study with the longest median follow-up (24 years) demonstrated that after the follow-up period, 68% of women with normal weight converted to unhealthy phenotypes [49]. In the Korean population, the percentage of metabolically healthy normal weight individuals who progressed to a metabolically unhealthy phenotype during the 4-year follow-up was 11.1% [50]. A study conducted in the Mexican population found that after 3 years of follow-up (±6 months), 53.6% of the metabolically healthy lean individuals remained in the same phenotype, while 18.5% converted to metabolically unhealthy lean, 18.4% to metabolically healthy obese and 9.5% to metabolically unhealthy obese [51]. The main predictors associated with a transition from metabolically healthy lean to metabolically unhealthy lean were male gender, age and number of pregnancies in women; conversely, a high socioeconomic status was associated with a decreased risk of progression. Kabat *et al.* conducted a 6-year study among postmenopausal women (Women's Health Initiative), in which they observed that the annual transition rate from the MHNW to MUNW phenotype was 0.026 (26 per 1000), and the annual transition rate from the MUNW to MHNW phenotype was 0.470 (470 per 1000) [52]. Women with MUNW returned to metabolic health much more frequently than metabolically unhealthy overweight and MUO women. The factors associated with the progression from the MHNW to MUNW phenotype comprised ethnicity (Hispanic or other vs white) and taking medication at follow-up to control diabetes, reduce cholesterol or control hypertension, while an increased probability of the transition from the MUNW to MHNW phenotype was associated with smoking and participation in the hormone therapy trial. However, the authors underline that their study was not designed to assess the effect of lifestyle or treatment as predictors of changes in metabolic health, which is why its results should be considered inconclusive. A long-term study showed that the risk of developing MetS in normal-weight subjects increased by 5% with each passing year (HR per year = 1.05; 1.03–1.06) [39]. In a cross-sectional study, the risk increased by 6% per year of age of the subjects [31]. An analysis conducted by Wildman on a model adjusted to confounding variables and WC showed that the risk of MONW at the age of 50–64 years was three times as high as the risk at the age of 20–34 years, and became almost four times higher at the age of ≥ 65 years [22]. In a Spanish population, the risk of MONW at the age of > 75 years was as much as 12.5 times higher than the risk at the age of 18–30 years [53]. Fan *et al.* also emphasised that the prevalence of MONW in women increased significantly after the age of 55 years, in contrast to men [34]. Consequently, the studies conducted among older age groups may indicate a higher prevalence of the phenotype in women than in men.

Characteristics of MONW

Subjects with MONW, in addition to metabolic disorders (i.e. the typical components of MetS specified in the NCEP ATP III and IDF definitions, such as dyslipidaemia, high glucose concentration, high BP and abdominal obesity) show high adiposity indices, i.e. high %BF, high accumulation of visceral adipose tissue, a high ratio of visceral and subcutaneous abdominal adipose tissue (VAT/SAT) and increased levels of liver and muscle fat despite having a normal weight [20, 54–57]. They also have a lower skeletal muscle percentage, reduced skeletal muscle mass ratio (skeletal muscle mass divided by body weight) and a lower level of muscular fitness [20, 44, 58] compared to slim and healthy subjects (MHNW). Many researchers have indicated that MONW is also characterised by decreased insulin sensitivity, and increased glycosylated haemoglobin concentration (HbA_{1c}) [40, 59]. Postprandial glucose and insulin were higher by 15% and 65%, respectively, among individuals with MONW than in the control group, while HbA_{1c} and fasting glucose did not differ between the groups [60]. Kim *et al.* observed that serum ferritin concentrations were positively associated with MONW [61]. Additionally, serum ferritin may be a predictor of impaired glucose metabolism, with high concentrations of serum ferritin correlating with obesity, type 2 diabetes, high BP, dyslipidaemia and the MetS. A serum ferritin level of 127.03 ng/ml in men and of 46.87 ng/ml in women were proposed as cut-off values for iden-

tification of MONW [61]. Furthermore, subjects with MONW showed high concentrations of inflammation biomarkers, including high-sensitivity C-reactive protein, interleukins IL-1, IL-6 and IL-8 and tumour necrosis factor (TNF-α) [62], as well as a high concentration of leptin [63] and a low concentration of adiponectin [40]. The MONW group had a higher risk of hypotestosteronaemia compared to the metabolically healthy group in a Chinese male population [64], while high oxidative stress was related to low concentrations of glutathione [65]. Postmenopausal women with MONW also displayed greater odds of having plasma oxidised low-density lipoprotein (LDL) and urinary 8-epi-prostaglandin F2α levels in the top quartile compared to women of a healthy normal weight [66]. A study of the metabolome conducted among subjects with MONW noted significantly lower concentrations of alanine, betaine, glycine, glutamine, histidine and L-glutathione in addition to higher concentrations of creatinine, cholic acid, isoleucine and L-proline compared to metabolically healthy subjects [14].

Developmental and genetic factors determining the occurrence of MONW

The MONW phenotype is observed in subjects even as young as children and youth [67–69], which suggests the existence of genetic and/or developmental predispositions for metabolic dysfunctions in normal-weight individuals. Li *et al.* reported that in normal-weight children from the Chinese population, the early environment, and especially a low birthweight, were significant predictors of MONW, defined as the presence of any one component of MetS [70]. Viitasalo *et al.* concluded that an increase in adiposity occurring between childhood and adulthood was a very strong predictor of MONW in adults [71]. In fact, every increase in the BMI by 1 standard deviation from childhood to adulthood led to a 2.5-times increase in the risk of MONW in adults. The results of a 2-year observation showed that for children whose adiposity increased on their entry into puberty, the risk of a metabolically unhealthy phenotype also increased despite maintaining a normal body mass [72]. Elías-López *et al.* found that an increase of VAT even in adult subjects who lost weight was associated with a higher risk of conversion to an unhealthy phenotype [51]. An increase in the severity of BMI by 1 kg/m^2 (defined as an individual's mean BMI from five consecutive measurements) was associated with a 1.23-times increase in the risk of MONW compared to MHNW and only with a 1.15-times increase in the risk of MUO compared to MHO [36]. Longer-lasting obesity was also associated with a higher risk of MONW. However, the authors of the study suggested that higher exposure to excess adiposity explained the increased risk of an unhealthy phenotype only partially.

However, few studies have been conducted to date that have directly addressed the development of the MONW phenotype. These studies suggest that four mechanisms are involved in the development of MONW: insulin resistance, insulin signalling, adipogenesis and distribution of adipose tissue [73]. Yagoothkar *et al.* demonstrated the existence of a cluster of 11 genetic variants in or near the genes: ANKRD55 (ankyrin repeat domain 55), ARL15 (factor 15 similar to ADP ribosylation), FAM13A (family with sequence similarity 13), GRB14 (growth factor receptor-bound 14), IRS1 (insulin receptor substrate 1), LYPLAL1 (lysophospholipase-like protein 1), PEPD (peptidase D), PDGFC (platelet-derived growth factor C), PPARG (peroxisome proliferator-activated receptor γ), RSPO3 (R-spondin 3) and TET2 (TET methylcytosine dioxygenase 2), which are associated with the metabolic traits (especially insulin resistance) that are responsible for the development of a lipodystrophy-like phenotype [74]. The lipodystrophy-like phenotype is characterised by an increased risk of arterial hypertension, type 2 diabetes and coronary artery disease, despite having a low BMI. The alleles of the aforementioned 11 loci that increase insulin resistance are correlated with a lowered BMI but also with increased concentrations of triglycerides (TG) and alanine transaminase (ALT) and increased liver steatosis, along with increased VAT/SAT and decreased concentrations of HDL-C, adiponectin and sex hormone-binding globulin. The authors also demonstrated that the genetic risk coefficient correlated more strongly with VAT/SAT than with BMI, which confirmed that a preferential accumulation of visceral fat is a more important risk factor for the development of MONW than generalised obesity.

A GWAS conducted among 49,915 individuals from the Korean population showed that MONW was associated with variants of the following genes: ABCB11, APOA5, APOC1, CDKAL1, CDKN2B, CETP, GCKR, LPL and NT5C2 [75]. Of these nine genes, only three (APOA5, CETP and LPL) were also associated with metabolically unhealthy phenotypes among obese individuals. APOA5, APOC1, CETP and LPL are associated with lipid metabolism, while ACBC1, CDKAL1, CDKN2B and GCKR are associated with glucose and insulin metabolism; and NT5C2 encodes hydrolase, which plays an important role in the cellular metabolism of purines and the regulation of uric acid. The single nucleotide polymorphisms (SNPs) of NT5C2 are also associated with a high BP. A study on two SNPs, rs2241766 and rs1501299, of the ADIPOQ gene conducted among the Han Chinese population showed that the minor allele T of the rs1501299 polymorphism correlated with a reduced risk of MUNW (OR = 0.63; p = 0.001) [76]. On the other hand, no significant correlation was found between MUNW and the rs2241766 polymorphism. Each additional C allele in the rs2206734 locus of the CDKAL1 gene (within the gene encoding the cyclin dependent ki-

nase 5 (CDK5) regulatory subunit-associated protein 1-like 1) reduced the risk of MONW in Chinese children by 21% [70]. Furthermore, in individuals with a high birthweight, each C allele at this locus was associated with a 62% reduced risk of MONW. However, no such association was found in the children with a low and intermediate birthweight. A study conducted among Iranian youth, which defined MONW as the presence of one cardiometabolic risk factor, analysed the prevalence of four polymorphisms of the genes involved in the regulation of lipid concentration [77]. The healthy youth showed a significantly lower prevalence of the tt minor allele of the GCKR (glucokinase regulatory protein) rs1260333 polymorphism and a higher prevalence of the cg and gg minor alleles of the MLXIPL (MLX-interacting protein-like, also known as the carbohydrate-responsive element-binding protein) rs3812316 polymorphism compared to the youth with MONW. The study also noted that the prevalence of the ga allele of the GCKR polymorphism (rs780094) was higher in those with MONW than among their obese peers with a cardiometabolic risk factor. The risk genotype AA rs9939609 of the FTO gene was more prevalent in the Iranian individuals with MONW than in slim and healthy individuals, but was less prevalent than in both groups with obesity (BMI > 30 kg/m^2) [78]. Consequently, the risk genotype correlated more strongly with obesity than with the metabolically unhealthy phenotypes.

Recent whole-genome studies have separated obesity from its comorbidities, allowing researchers to distinguish between metabolically 'harmful' obesity and metabolically 'rather beneficial' obesity with a fairly good accuracy, as well as to identify the loci of beneficial obesity [79–81]. Consequently, the corresponding loci for MONW can be expected to exist; in fact, some studies have already confirmed their existence [77]. Sulc *et al*. explained that the genetic variants affecting the BMI operate primarily through the central nervous system, which involves regulating the human appetite and energy balance, whereas the genetic influence on the Waist/hip ratio (WHR) adjusted for the BMI likely takes places mostly through adipose tissue and involves adipogenesis and insulin signalling [80]. There may also exist genetic variants that determine the occurrence of metabolic disorders but are not associated with adiposity. Thus, the genetic causes of MONW require further research. It should be underlined that difficulties related to determining these causes result from the complexity of the components involved in MONW, as well as a lack of uniform definition and major heterogeneity between different ethnic groups.

Smoking

A long-term observation study conducted by Bradshaw *et al*. showed that over a nine-year follow-up period, current smoking patterns correlated positively with MONW (HR = 1.38; 1.15–1.66), but similar associations were also found in the overweight and obese groups [39]. Most cross-sectional studies have confirmed that smoking is associated with lowered metabolic health and an increased risk of MONW [19, 28, 41, 53], although a few studies did not observe such a correlation [13, 23]. Furthermore, one study found that current smoking practices were associated with lowered metabolic health only in normal-weight and overweight individuals, but not in those with obesity [21]. Another study even showed that a positive correlation between smoking and metabolic disorders only occurred in normal-weight participants, and not in the overweight or obese participants [28]. The results of these two studies suggest that the effect of smoking on the occurrence of metabolic disorders is stronger in normal-weight individuals than in overweight or obese individuals.

Alcohol consumption

A 9-year follow-up showed that the risk of MONW was lower in individuals who consumed moderate and high amounts of alcohol compared to non-drinkers or rare drinkers [39]. In a study conducted among the Chilean population, increased risk of an unhealthy phenotype in normal-weight individuals also correlated with the lowest tercile of alcohol consumption [44]. Likewise, in a study conducted among the Korean population, the individuals who consumed moderate amounts of alcohol (≤ 2 drinks per day) were less predisposed to MONW than non-drinkers [37]. In many other studies, the association between alcohol consumption and MONW was either insignificant [31], or was found only in non-adjusted models and became statistically insignificant after the inclusion of confounding variables [22, 53]. In the Brazilian population, higher alcohol consumption (≥ 140 g/week for women and ≥ 210 g/week for men) correlated with a metabolically unhealthy phenotype [19]. In some studies, the correlation between alcohol consumption and MONW was not analysed at all [21]. The main problem with assessing the correlation between alcohol consumption and MONW is the lack of a uniform definition for this phenotype. Furthermore, alcohol may affect each metabolic disorder differently, and 'moderate' consumption is also defined differently among the studies.

Diet

Both long-term studies [82] and meta-analyses [83] confirmed that diet plays an important role in the development of MetS and its components. However, there are few studies analysing diet that have focused on individuals with MONW.

Dietary patterns (DP)

Subject literature emphasises that analysing DP may be more useful for the assessment of correlations

between diet and risk of chronic diseases than analysing associations with individual groups of products or nutrients because DP reflects the complexity of a diet better. An assessment of DP conducted with 2479 subjects with MONW among the Polish population (BMI = 18.5–24.9 kg/m^2) showed that a 'prudent dietary pattern', including a high amount of fish and whole-grain products and a low amount of refined products, potatoes, sugar, sweets and processed meat, correlated significantly with a lower risk of MONW, high glucose concentration and low HDL-C concentration [84]. Low diet quality and high adherence to 'Western' DP were independent predictors of poor metabolic health among young adults, aged 18–35 years, regardless the of BMI and WHR [85]. The study defined 'Western' DP as involving frequent consumption of processed meat, red meats, animal fats and other edible fats, potatoes, refined grain products, sugar, sweetened beverages and alcohol. A study conducted among Australian adults confirmed that healthy DP correlated significantly with metabolic and BMI phenotypes [86]. The odds of having a metabolically healthier profile increased by 16% for every one standard deviation increase in the healthy DP. However, the study analysed individuals with a normal BMI and those with overweight jointly. Conversely, none of the three DP identified among the Brazilian population correlated significantly with MONW [87]. Consequently, it is impossible to determine whether the DP in individuals with MONW differ significantly from the DP in individuals with MUO.

Following dietary recommendations

Another approach to assessing DP and the relationship between diet and health is to evaluate dietary recommendations based on the established dietary indexes (e.g. the Healthy Eating Index, HEI) or adherence to a particular diet (e.g. Dietary Approaches to Stop Hypertension, DASH) [51, 88, 89] or a food pyramid [13].

An observation conducted among subjects with MONW, lasting for an average of 18.6 years, found that an increase by 1 standard deviation (i.e. by 2 points on a scale from 0 to 9) in their adherence to the DASH diet or HEI (by 14 points on a scale from 0 to 100) correlated significantly with a reduction of mortality from any cause by 17% and 22%, respectively [88]. Furthermore, a DASH score analysis showed that in subjects with MONW, the percentage of energy obtained from saturated fatty acids and the total fat and potassium content in the diet were higher than in metabolically healthy subjects. Likewise, the results of the HEI were higher for lipids, saturated fatty acids and cholesterol and were lower for dairy products and food variety in the MONW group than in the control groups. In a long-term study conducted among the Mexican population, diet only significantly affected conversion to an unhealthy phenotype in a group of individuals with obesity, and not in a group of normal-weight individuals [51].

A cross-sectional study conducted in a population representative for the US (Third National Health and Nutrition Examination Survey, NHANES III) confirmed that the DASH index correlated inversely with MONW, but only in the younger age group, which included men < 45 years and pre-menopausal women [89]. In terms of the components of the DASH index, the consumption of fibre and magnesium was found to be significantly lower in the MONW group than in the control group (MHNW). The Mediterranean diet index also indicated the same association with MONW as the DASH index, but with no statistical significance. Phillips *et al.* analysed data from a Mitchelstown cohort and concluded that a higher quality of diet and adherence to a food pyramid correlated positively with metabolic health in individuals with a BMI < 30 kg/m^2, but only in the non-adjusted model [13].

Intake of food groups

The results of a prospective study suggest that the consumption of some food groups in adults may lead to a transition to a metabolically unhealthy phenotype, regardless of BMI [32]. Overall, more such relationships were observed in a group with overweight and obesity, which suggests that the effect of diet on the conversion to a metabolically unhealthy phenotype is stronger in individuals with overweight and obesity than in normal-weight individuals. However, some dietary determinants of a metabolically unhealthy phenotype were found to be more important in the normal-weight group. In an adjusted model, each increase by one standard deviation in the consumption of potatoes and processed meats was related to a significantly increased risk of a metabolically unhealthy phenotype by 31% and 43%, respectively, in the normal-weight group and by only 14% and 7% in the group with overweight and obesity.

In a cross-sectional study conducted in Chile, the highest consumption of fruits and vegetables (> 4.0 portions/day vs. 0 to 1.4 portions/day) and of fish and seafood (1 to < 3 times/month vs. < 1 time/month; OR = 0.16; 0.03–0.90) correlated with a lower risk of MONW in young adults (OR = 0.05; 0.01–0.40) [44]. Likewise, in children and youth from the Chinese population aged 6–18 years, higher consumption of fruits reduced the risk of MONW by 25% (p = 0.018) [70]. Van Hulst *et al.* conducted a two-year observation of normal-weight children aged 8–10 years from the Canadian QUALITY cohort. They also found a trend toward a lower risk of metabolic disorders associated with a higher consumption of fruits and vegetables [72], but with no statistical significance. An Iranian population showed a higher consumption of meat in adults with MONW than in adults without MONW

[90]. However, no differences in the consumption of fruits and vegetables were found between the two groups. A higher consumption of meat and a lower consumption of dairy products also correlated with higher insulin resistance indexes. In a recent study conducted among the Chinese population, the MONW phenotype was positively associated with higher red meat consumption (≥ 2 kg per week, mainly beef and mutton) and was inversely associated with vegetable consumption (≥ 4 plates per week, for a plate with a diameter of 16 cm) [35].

Intake of nutrients

The intake of energy and macronutrients over a 5-year observation period was not significantly associated with the development of an unhealthy phenotype in normal-weight individuals or individuals with overweight and obesity [32]. However, the same study found that the risk of MONW increased by as much as 24% per one standard deviation increase in the consumption of sodium, while the risk of MUO increased only by 15%, with the effect in the latter group being statistically insignificant. Likewise, it was observed that increased consumption of nutrients such as potassium, calcium and vitamin A significantly reduced the risk of MONW, with no such effect occurring in the group with overweight and obesity. The diets of women with MONW from the Korean population displayed a significantly higher saturated fatty acids content (11.6 ±1.36 g vs. 16.7 ±2.20 g), with a lower amount of polyunsaturated and saturated fatty acids (1.38 ±0.18 vs. 0.76 ±0.13) and a lower intake of dietary fibre (16.5 ±1.01 g vs. 12.2 ±1.08 g) compared to women from the control group [63]. A different study conducted among the same population found that a high-carbohydrate diet (≥ 73.9% of energy intake) correlated with a higher risk of MONW than a low-carbohydrate diet, whereas a high-protein diet (≥ 17.1% of the energy intake) correlated with a lower risk of MONW than a low-protein diet (< 12.2% of the energy intake), but only in women [91]. Among Black South Africans, the total consumption of protein, fat, palmitoleic acid and arachidonic acid was higher in a group with MONW than in a group with MHNW. However, similar differences were noted between the MUO and MHO phenotypes [45]. According to the authors of the study, the differences resulted from higher consumption of meat in both groups with metabolic disorders.

Nier *et al.* assessed children aged 5–9 years and found that despite a similar intake of calories and macronutrients, the total consumption of fructose and glucose (primarily from drinks with added sugar, fruits and vegetables) was higher in normal-weight children with metabolic disorders than in healthy children [92]. Phillips *et al.* concluded that the intake of calories and content of macronutrients in the diet were similar between metabolically healthy and unhealthy individuals, regardless of their BMI [13]. Conversely, an Iranian population displayed a higher calorie intake and fat consumption in adult men with MONW than in those without MONW [90]. On the other hand, the two groups displayed no differences in the consumption of protein, carbohydrates or fibre. Meanwhile, Abolnezhadian *et al.* observed no significant differences in the consumption of nutrients between the four metabolic phenotypes that they analysed [78]. A recent study revealed that each 10% increase in total energy intake in women corresponded to a 1.37-times increase in the risk of MetS [93]. An increase of 10% in the total consumption of protein also correlated with a 1.21-times higher risk of MetS, although this effect concerned primarily animal protein, rather than plant protein. On the other hand, no significant differences were observed between the different metabolic phenotypes. Total consumption of flavonoids and each class of flavan-3-ols, flavonols, and flavones correlated inversely with the development of an unhealthy phenotype both in normal-weight individuals and in individuals with overweight and obesity [94]. Conversely, consumption of anthocyanins, total carotenoids, β-carotene, lutein and zeaxanthin was significantly associated with a lower risk of an unhealthy metabolic phenotype only among normal-weight individuals.

Nutrient concentration in the serum

The analysis of fatty acid concentrations in the plasma indicated that the MONW group showed a lower concentration of very long-chain saturated and monounsaturated fatty acids and linoleic acid than the MHNW group [45]. Subjects with MONW aged ≥ 40 had lower concentrations of 25(OH)D compared to healthy subjects [95]. Furthermore, among the subjects with a vitamin D deficiency, the MONW group showed an increased risk of abdominal obesity (OR = 3.28; p = 0.005), arterial hypertension (OR = 3.08; p = 0.003) and increased C-reactive protein (OR = 1.97; p = 0.03). In a study conducted among children and youth, the risk of being 'metabolically non-healthy non-obese' (MNHNO) decreased significantly by 7% per each unit of an increase in the 25(OH)D concentration (ng/ml) compared to their healthy peers [96]. In another study it was observed that the presence of the MONW correlated positively with hypomagnesaemia (OR = 6.4; 95% CI: 2.3–20.4) [97]. The application of 382 mg of magnesium over 4 months led to a significant increase in HDL-C concentration and a decrease in TG concentration in the subjects with both MONW and hypomagnesaemia compared to the placebo group [98]. However, a study conducted among the Polish population found a positive correlation between increased calcium concentration along with decreased phosphorus in the serum and MetS in

normal-weight subjects, but no correlation was found between the vitamin D concentration and MetS in the same group [99]. The authors of the study suggested that this unexpected positive correlation between increased calcium concentration and MONW may have resulted from the fact that hyperglycaemia and a high BP alter the concentration and metabolism of calcium.

Dietary habits

Conus *et al.* used the Three-Factor Eating Questionnaire to assess dietary habits and found that women with MONW showed a lower level of dietary restraint than women from the control (non-MONW) group. However, they found no differences in the factors of disinhibition, hunger or food intake between the two groups [100].

Caloric restriction (CR) and intermittent fasting (IF)

Trials conducted with both animals and humans have confirmed the numerous benefits to health provided by CR. These benefits include decreased energy expenditure, improved function of the mitochondria, decreased oxidative stress, decreased inflammatory markers and improved metabolic and hormonal risk factors, which are engaged in the pathogenesis of type 2 diabetes, cardiovascular diseases (CVDs) and tumours [101, 102]. However, the majority of such trials were conducted among obese individuals. A study conducted among the Korean population showed that 19.6% of men and 37.8% of women with a BMI < 25 kg/m^2 attempted to lose weight [103]. The men with MONW attempted to lose weight more often than the men without MONW (23.6% vs. 18.8%), while the reverse was true for women (27.3% vs. 39.3%). Awareness of one's metabolic health was also found to be a significant factor in making the decision to lose weight, because within the MONW group, the subjects with a high number of MetS components had a higher likelihood of attempting to lose weight than the subjects with a low number of MetS. The study conducted among MONW Asian subjects (BMI = 22.7 ±0.4 kg/m^2, aged 48 ±3 years old) showed that a 5% diet-induced weight loss caused reduction of total fat mass by 9%, visceral fat volume by 11% and intrahepatic fat by 50% [104]. Significant improvements in the lipid profile (i.e. lowering of total cholesterol, LDL cholesterol and TG), improvement in insulin sensitivity, and lowering of diastolic blood pressure were also observed. The CALERIE 2 program evaluated the effect of 24-month-long CR (a reduction by 25% of the energy demand) on CVD and insulin resistance risk factors in healthy, non-obese subjects (BMI = 22–28 kg/m^2) [105]. The authors concluded that a continuous CR significantly improved the metabolic risk factors in the study subjects, including the VAT mass, BP, lipid profile and ectopic lipid accumulation. However, the improvement in insulin sensitivity was only temporary.

Intermittent fasting has emerged in recent years as a popular, unconventional method of both losing weight and improving one's metabolic health [102]. Currently, the term refers primarily to therapeutic interventions aimed at temporarily reducing the intake of food. The four most popular types of IF are: the 5 : 2 diet (2 days of limited energy each week and eating *ad libitum* for the other 5 days); time-restricted feeding (TRF; eating limited to a specific time window, usually lasting ≤ 10 h, and night-time fasting extended to at least 14 h); alternate-day fasting (ADF; complete fasting every other day); alternate-day modified fasting (ADMF; limited energy intake every other day, but one meal is allowed when fasting to the amount of about 25% of the energy demand, usually eaten at noon) [102, 106]. Most types of fasting reduce the total number of hours available for eating, thus potentially reducing the total calorie intake. Consequently, weight loss is achieved fairly often with IF; however, it seems that IF also provides cardiometabolic benefits other than those resulting from weight loss alone. Interventions involving IF have helped to activate the adaptive cellular responses developed through evolution that optimise metabolism by improving the glucose and insulin regulation, BP, resting heart rate, HDL, LDL and TG concentrations and by reducing oxidative damage and inflammation [107, 108]. Anton *et al.* stated that exhausting the reserves of glycogen in the liver and the resulting shift towards the metabolism of endogenous lipid-derived substrates (ketone bodies, glycerine and non-esterified fatty acids) activates a set of adaptive processes that improve a person's health, including their body composition [109]. However, as with CR, most studies on the effects of IF on the body have been conducted among subjects with obesity. Harvie and Hovell stated that short-term trials showed potential, albeit sometimes unclear, benefits from the application of IF and intermittend energy restriction in normal-weight and overweight subjects. In some trials, the same effects were also observed without an overall reduction in calorie intake [110].

Sixteen healthy subjects (with a BMI ranging from 20.0 to 30.0 kg/m^2) who used ADF for 22 days showed a decrease in their body weight by 2.5%, fat mass by 4% and fasting insulin by 57% [111]. Varady *et al.* investigated the effect of ADF on the coronary heart disease risk among subjects with a BMI = 20.0–29.9 kg/m^2 [112]. Following a 12-day intervention, the authors observed a decreased fat mass and an improvement in the TG, C-reactive ptotein (CRP), leptin and adiponectin concentrations, while the LDL, HDL, homocysteine and resistin concentrations did not change. Another randomised study conducted an intervention among non-obese subjects that involved alternating between days of fasting with 25% of the normal caloric intake and days of feasting with 175% of the normal caloric intake [113]. After 3 weeks, a minor increase

(by 2.7%) was observed in the expression of the SIRT3 gene, which may play a key role in the mechanism that underlies the beneficial effects of a reduced calorie intake. Intermittent fasting also reduced the insulin concentration in the serum (1.01 μU/ml). On the other hand, no changes were found in the expression of other genes or oxidative stress markers.

Some studies showed that IF, in addition to reducing the %BF and providing certain metabolic benefits, also decreased the lean mass [114, 115], in contrast to other studies which did not observe this effect [112, 116]. One study demonstrated that some metabolic markers for muscles responded differently to fasting, depending on the adiposity. Obese individuals showed lower breakdown and synthesis of the proteins of the skeletal muscles of the forearm after both 12 and 72 h of fasting compared to lean individuals [117].

Observational studies were also conducted to analyse the health-related effects of religious fasting, e.g. fasting from sunrise to sunset during Ramadan, which involves eating one large meal after sunset and one light meal before sunrise. Thus, the period of fasting lasts for about 12 h. However, to our knowledge, no study to date has assessed its effect on the health of individuals with MONW.

Physical activity

Many authors have pointed out the problem of low physical activity in individuals with MONW as a factor predisposing them to increased accumulation of fat, especially abdominal fat. A long-term observation showed that the risk of metabolic disorders was significantly lower in normal-weight adults in the third (the highest) tercile of physical activity than those in the first tercile [39]. Individuals with a normal BMI diagnosed as healthy at baseline, who developed ≥ 3 components of MetS over a 4-year-long prospective observation, were physically less active than the individuals who remained healthy [50]. Likewise, physical activity observed during a long-term study did not significantly correlate with the transition from MONW (defined as meeting one or more criteria of MetS, excluding abdominal obesity) into a healthy phenotype (MHNW) [118]. In a cross-sectional study the post-exercise energy expenditure (PAEE) was significantly lower in women with MONW than in healthy women (2.66 ±0.92 vs. 4.39 ±1.50 MJ/day), which amounted to a difference of 1.16 MJ/day (412 kcal/day) [119]. Conus *et al.* also observed a lowered PAEE in women with MONW [100]. The lower PAEE in individuals with MONW may have contributed to a positive energy balance, and consequently, to an increase in total fat mass, affecting insulin sensitivity and other risk factors.

Among the Korean population, adult individuals who spent more time on moderate-intensity exercises were less predisposed to MONW [37]. In a study conducted by Park *et al.*, the older age group of U.S. adults (men ≥ 45 years and postmenopausal women) with MONW included over twice as many physically inactive individuals than the group with MHNW (21.0% vs. 10.3%) [88]. Samouda *et al.* assessed men and women aged 25–64 years and found that every 100 METs (metabolic equivalents of task per minute) of higher transport-related physical activity correlated with a 2% lower risk of MONW than MHNW [31]. Individuals with MHNW performed aerobic exercise the most often (83%) among all the analysed phenotypes. The MHNW group also exhibited much fewer functional physical limitations than the MONW group. In a study conducted in Poland, the correlations between physical activity and the risk of MetS components were the strongest in overweight and obese subjects. However, subjects with a normal BMI who self-reported low levels of physical activity also displayed a significantly higher risk of MetS compared to those who reported vigorous levels of physical activity (OR = 1.45; 1.17–1.88) [120]. A longer sitting time only increased the risk of abdominal obesity, in both the normal-weight and the overweight and obese group. The Icaria study also found that the percentage of individuals with a sedentary lifestyle was higher in the MONW group than in the MHNW group (59.2% vs. 51.1%) [42].

A longitudinal study confirmed that an increased screen time over a two-year follow-up period in children aged 8–10 years correlated with a higher risk of MONW, defined as a BMI below the 85th percentile for the child's age and sex and the presence of at least one cardiometabolic risk factor [72]. An analysis of data from the International Children's Accelerometry Database indicated that a higher amount of objectively measured moderate-to-vigorous physical activity was beneficial for both metabolic health and body weight, whereas a shorter sitting time was only beneficial for metabolic health [121].

The relationship between low PA and the risk of MONW is confirmed by cross-sectional studies and two [39, 53] of the four long-term studies [39, 50, 53, 118]. The primary limitation in the assessment of the effect of PA on the risk of MONW is the fact that each study used different definitions, intensities and measurement tools for PA, which makes it impossible to compare and generalise the results and reach unambiguous conclusions.

Sleep duration

In Korean adults, sleep duration differed significantly depending on the body mass and metabolic phenotype, but did not differ between individuals with MHNW and MONW [122]. Conversely, in children and youth, a very short sleep duration (≤ 5 h) compared to a normal duration (8–10 h) correlated with a lower risk of MONW (OR = 0.478; 0.237–0.962),

whereas a longer duration (≥ 11 h) correlated with a higher risk of MONW (OR = 2.581; 1.124–5.928) [123]. Sleep deprivation stimulates certain parts of the brain that are sensitive to food-related stimuli. Consequently, sleep-deprived individuals may choose calorie-rich foods and develop obesity. Furthermore, research indicates that a short sleep duration is associated with an increased concentration of ghrelin, which increases the appetite, and a reduced release of leptin, a hormone that decreases appetite [124]. Some studies also suggest that a long sleep can increase the risk of metabolic disorders because it is often associated with low physical activity, low quality of sleep, sleep disorders, bad health and low socioeconomic status [125].

Conclusions

The prevalence of MONW is estimated to range from 1.0% to 28.6% between different populations, depending on the age of the study participants and the definition of MONW used in the study. Adopting a uniform definition would allow researchers to compare the prevalence of MONW between different populations and to monitor the long-term changes related to it.

Difficulties related to determining the genetic causes of MONW result primarily from the lack of a uniform definition and from the complexity of the disorder. Each component of MONW may be determined by different genes. Lifestyle, in particular diet, seems to be a significant factor in the development of MONW, but to date, research has not determined the optimal type or duration of the dietary intervention needed to improve the metabolic parameters in individuals with MONW. However, the dietary recommendations aimed at preventing MONW should take into account the fact that the effect of DP on the risk of metabolic disorders may differ depending on an individual's racial origin and genetic predispositions [126]. Current evidence points to a DASH diet as the best recommendation for individuals with MONW.

Some studies have shown that weight loss may improve the profile of metabolic risk, even in individuals with MONW, and reduce the risk of a transition from a metabolically healthy to an unhealthy phenotype [127]. Nonetheless, further research needs to be conducted concerning the viability of IF and CR in individuals with MONW, because a long-term application IF and CR may prove to be harmful by potentially reducing the skeletal muscle mass [104, 128]. Reducing the sitting time seems to be an important part of MONW prevention. However, it is again necessary to establish the exact or minimal volume of activity (duration and intensity) needed for individuals with MONW to obtain the desired health benefits.

Further observations are required, preferably long-term ones, that would allow for the assessment of modifiable risk factors responsible for the transition from a metabolically healthy to an unhealthy phenotype, as well as factors affecting the return to metabolic health.

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Conflict of interest

The authors declare no conflict of interest.

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