

Review

Obesity vs. Metabolically Healthy Obesity in East Asia

Bryan J. Mathis ^{1,*} , Kiyoji Tanaka ² and Yuji Hiramatsu ¹¹ International Medical Center, University of Tsukuba Hospital, Tsukuba 305-8576, Japan² Faculty of Health and Sport Sciences, University of Tsukuba, Tsukuba 305-8575, Japan

* Correspondence: bmathis@md.tsukuba.ac.jp; Tel.: +81-29-853-3004

Abstract: With over one-third of East Asia's 1.7 billion people overweight or obese, mounting demographic pressure and burgeoning healthcare costs are forcing public health officials to grapple with the rising morbidity and mortality associated with obesity. However, the presence of metabolically healthy obesity, in which the short-term disease risks of diabetes and heart disease are low, represents a possible buffer for healthcare planning in East Asia. This narrative review analyzes the health risks from obesity through representative Japan- and China-specific analyses that take into account unique cultural, genetic, and other factors that drive obesity; the potential impact of metabolically healthy obesity on public health; and suggested non-surgical/non-pharmacological interventions to relieve pressure on the nationalized healthcare systems prevalent in the region. Such an emphasis on interventions to both delay obesity as well as potentially reverse metabolic syndrome could save millions of lives and billions of USD equivalents in healthcare throughout East Asia.

Keywords: metabolically healthy obesity; diabetes; Asia; Japan; China; public health

1. Introduction

1.1. Asian Obesity: A Focus on Metabolic Health

The Crisis Point: Expected Life and Public Costs for East Asia

Obesity-related risks mainly consist of cardiorespiratory, cerebrovascular, and metabolic diseases (such as heart failure, stroke, and diabetes) [1]. Such obesity-related issues require both long-term intervention (e.g., insulin and monitoring for diabetes) as well as eventual invasive surgery for cardiorespiratory diseases or strokes [1]. Furthermore, lost productivity from reduced functional capacity and medical recovery after procedures can drain thousands of USD equivalents per patient per year from an industrialized economy [2].

Obesity will be a major drain on East Asian regional healthcare expenditures over the next 20 years since direct disease expenditures stemming from overweight/obese conditions already cost 0.78% of the GDP (or up to a pan-Asian average of 12% of healthcare costs annually) and as morbidity rates rise steadily throughout the region [3]. Indirect costs, based on years of productive lifespan lost due to obesity-related illness, may reach as high as USD 32 billion in China, while countries with smaller populations, such as South Korea or Japan, may have costs in the range of USD 800 million to USD 2 billion [3]. Yet another critical inflection point for Asia is the rapid aging of the current economic powerhouses of China, South Korea, and Japan, each with declining birthrates and increases in the percentage of population above age 65. In Japan, where 27% of the population is past retirement age, birthrates have not increased to compensate [4]. China is also projected to double its older adult population from 7% to 14% within 23 years, while Korea was already reported at 14% and increasing in 2017 [5,6]. In all cases, the burden of care for these rapidly aging societies will be magnified by obesity-related illnesses and decreases in functional status within both the working and retired populations.



Citation: Mathis, B.J.; Tanaka, K.; Hiramatsu, Y. Obesity vs. Metabolically Healthy Obesity in East Asia. *Encyclopedia* **2023**, *3*, 730–745. <https://doi.org/10.3390/encyclopedia3020053>

Academic Editors: Antonio Cicchella and Raffaele Barretta

Received: 27 April 2023

Revised: 1 June 2023

Accepted: 9 June 2023

Published: 12 June 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1.2. Obesity, Diabetes, the Heart, and the Brain: A Troublesome Tetrad

Obesity has been linked to the development of type 2 diabetes and hypertension that precedes cardiovascular problems such as hypertension, coronary heart disease, and cerebrovascular maladies (i.e., stroke) [7]. The chance of developing these problems rises steadily as the obese person ages, with sarcopenia, non-alcoholic fatty liver disease (NAFLD), and metabolic slowdown contributing to the persistence of excess visceral body fat that maintains the increased risk [8–10]. Prediabetes may also be present and persist over the development of obesity, as evidenced through higher homeostasis model of insulin resistance (HOMA-IR) scores without other metabolic syndrome elements [11]. The effect of prediabetes as a chronically elevated glycemic state may cause inflammation and vascular damage that increases heart failure risk even if type 2 diabetes does not fully manifest [12].

Chronic cardiovascular and cerebrovascular conditions are thought to be caused by the synergistic effect of diabetes or prediabetes with hypertension on forming calcified arterial plaques, especially in the coronary and cerebral arteries [12,13]. This metabolism–disease relationship is proven by reports that mortality risks decrease observably upon loss of fat from the central trunk [14–17]. Furthermore, studies of glucose-controlling drugs that result in smaller waistline circumference and large population studies have observed decreased odds ratios of diabetic and cardiovascular risks after moderate weight loss [14,18]. These decreases are due to improvements in insulin sensitivity and resolution of NAFLD [19]. Reductions in renin-angiotensin activation, increased sympathetic tone, lower inflammation, and less oxidative stress also accompany fat loss and greatly reduce the risks of hypertension and pathologic cardiac remodeling in the previously obese [20].

1.3. General Interventions Available against Obesity

Clinical interventions such as medication to restore glucose sensitivity and bariatric surgery to limit caloric intake have met with some long-term success, but physiological/psychological side effects from medication and the invasiveness of surgery could be suboptimal for a significant portion of the younger obese population [21]. Furthermore, public health costs to provide medication and surgery plus long-term follow-up for tens of millions of patients may be unfeasible for East Asian healthcare systems already under strain from demographic pressure. For these reasons, exercise and diet remain a mainstay treatment that could save money by precluding millions of new prescriptions or surgeries.

As most East Asian countries have some kind of nationalized healthcare, supervised diet and exercise interventions may be the most financially suitable, but disparities in coverage, diet quality, and exercise feasibility (due to pollution) as well as cultural differences make general recommendations difficult. In this review, customized, non-pharmacological, and non-surgical intervention plans are suggested based on analyses of two representative countries, China and Japan.

2. Obesity and Metabolically Healthy Obesity Criteria: Impact

Obesity by BMI: The WHO and International Obesity Task Force

The Asian obesity pandemic was initially marked by controversy over its definition. For obesity in the West, WHO guidelines indicate that body mass index (BMI; a ratio based on kg of mass per square meter of body surface) values of 25.0 kg/m² or higher are indicative of overweight status, while a BMI of 30.0 kg/m² or higher indicates Class I obesity (Table 1a) [22,23]. According to these guidelines, obesity prevalence in East Asia would only be around 2–4% compared to 10–20% in the West, but studies showing similar glucose intolerance in Asian women with BMIs of 23 kg/m² or higher and Western women with BMIs of 25 kg/m² or higher have led to International Obesity Task Force recommendations that the overweight and obese BMI cutoffs for Eastern Asians be revised to 23.0 kg/m² and 25.0 kg/m², respectively (Table 1a) [24–26]. In light of these suggested revisions, overweight/obesity rates of around 20–30% of adults have been observed in the East Asian region, which is comparable to the West [3,27,28].

Pairing BMI classes with the Edmonton Obesity Staging System (EOSS) (Figure 1) better reflects the impact on quality of life as obesity progresses to metabolic diseases [29]. This combined system gives enhanced detail on the physical and mental condition of an obese patient (Table 1b). Based on physiological state, risk factors, and psychological limitations, the EOSS is divided into five stages, with stage 0 reflecting obesity with risk factors at a subclinical level (e.g., borderline high blood pressure) but with no debilitating symptoms or limitations [29]. By the time a patient reaches stage 2 and progresses to stage 3, significant medical needs, organ damage, and functional impairment exist, and reversing the obesity without surgical or pharmaceutical intervention becomes exponentially more difficult (Table 1b) [29]. Although reports that stratify Eastern Asian obesity based on the EOSS criteria of risk factors and medical care are scarce, a majority of Eastern Asian obese would be logically classified as stage 1 or 2 (e.g., suffering from high blood pressure, pre-diabetes, or kinesthetic limitations), while the subpopulation of obese with subclinical symptoms (e.g., elevated triglycerides or borderline high blood pressure) but no other metabolic diseases or functional limitations would be considered at stage 0, with progression into advanced stages occurring over a span of 5 to 10 years (Figure 1) [22,30].

Table 1. (a) WHO Obesity Classifications Based on BMI. (b) EOSS Stages and Criteria [31].

(a)		
BMI in kg/m ²		
Class	BMI–Non-Asian	Asian
Underweight	<18.5	<18.5
Normal	18.5–24.9	18.5–22.9
Pre-Obese	25.0–29.9	23–24.9
Class I	30.0–34.9	25–29.9
Class II	35.0–39.9	≤30
Class III	≤40	

(b)				
Stage	Grade	Mental Symptoms	Functional Limits	Medical Condition
0	Mild	None	None	None
1	Mild	No quality of life impact	Aches and pains, some dyspnea during exercise	No active diseases but subclinical markers (borderline high blood pressure, high cholesterol, abnormal liver enzymes)
2	Moderate	Depression, anxiety, low self-esteem	Limits on daily activities	Type 2 diabetes, NAFLD, sleep apnea, etc.
3	Significant	Chronic depression/anxiety, suicidal thoughts	Reduced mobility, reduced work capacity	Severe diabetes, organ damage, gout or joint damage
4	Severe	Psychologically disabled	Immobile, unable to work	End-stage organ failures, uncontrolled diabetes

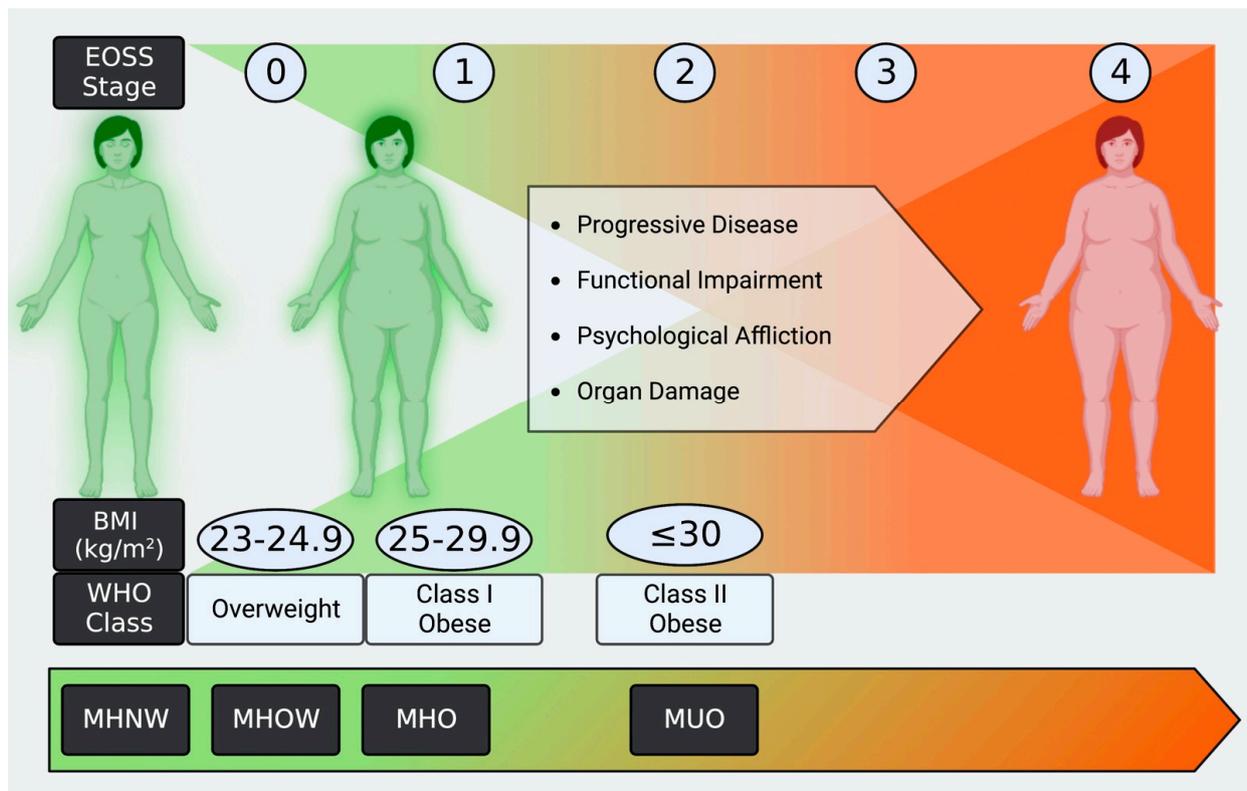


Figure 1. The Progression of Obesity and Disease in Asians [29,32]. Asians may develop obesity while maintaining metabolic health, but as time progresses, the majority will experience worsening physiological, functional, and psychological impairment as the BMI rises and metabolic health declines. MHW = Metabolically healthy normal weight; EOSS = Edmonton Obesity Staging System; BMI = Body mass index; WHO = World Health Organization; MHOW = Metabolically healthy overweight; MHO = Metabolically healthy obese; MUO = Metabolically unhealthy obesity. Created in [BioRender.com](https://www.biorender.com). (accessed on 27 April 2023).

3. Metabolically Healthy Obesity

3.1. What Is Metabolically Healthy Obesity?

Metabolically healthy obesity (MHO) is thought to be a transition state where biochemical stresses from excess body fat have not yet overcome homeostatic mechanisms in sugar metabolism. MHO patients are overweight by body mass index (BMI) guidelines yet maintain normal glucose metabolism, low systemic inflammation, and normal cardiometabolic profiles (EOSS stage 0) [22,29]. MHO does not carry the same short-to-medium-term risks of cardiovascular or diabetic events as metabolically unhealthy obesity (MUO), but this is predicated on maintaining a stable MHO status [31]. As time under the obese condition passes, disruptions in homeostasis from reactive oxygen species, loss of aerobic fitness, glucose dysregulation, excessive inflammation, and hormonal signaling (especially leptin-ghrelin resistance) increase the risk of initiating a progressive cascade of metabolic damage that damages organs and results in diabetes and hypertension [33]. Thus, prevention of destabilized obesity (MUO) is of paramount importance for East Asia.

Biochemically, progressive increases from baseline in blood pressure, blood triglycerides/cholesterol, waist circumference, pro-inflammatory cytokines (e.g., $\text{TNF}\alpha$, $\text{IFN}\gamma$, and GM-CSF), and reactive oxygen species (e.g., nitrotyrosine as measured by mass spectrometry) stemming from uncontrolled blood sugar can be measured to delineate the pathogenesis of MUO from an MHO state (Table 2) [34–38]. Further population-level studies are needed to fine tune the thresholds of MHO and MUO in the sub-populations

that comprise the pan-Asian region (e.g., Han Chinese versus the indigenous Iban people of Malaysia), which may differ due to variations in genetics, culture, and physiology.

Table 2. MHO Definition by Clinical Parameters.

Criteria	Thresholds	Reference
Blood Pressure	Systolic \leq 130 mmHg Diastolic \leq 85 mmHg	[29,31]
Glucose Metabolism	Fasting \leq 6.1 mmol/L No type II diabetes	[29,31]
Serum Triglycerides	Fasting \leq 1.7 mmol/L	[31]
HDL-C	>1.0 mmol/L for men >1.3 mmol/L for women	[31]
Waist Circumference (Waist-to-Hip Ratio)	<0.95 for women <1.03 for men	[29]
Inflammatory Biomarkers (TNF α , IL-6)	Nominal	[39,40]
Body Mass Index	\geq 30 kg/m ² Western \geq 25 kg/m ² Asian	[26,31]

3.2. MHO Effect on Type 2 Diabetes and Cardiovascular Disease Risks

Longitudinal studies of large populations in Asia report that MHO status should not imply a total absence of disease risk but rather a temporary reduction in short-term risk during which stabilizing interventions can take place before metabolic or cardiovascular disease pathogenesis. Again, reports verify the presence of unstable biomarkers (inflammation, abdominal obesity, dyslipidemia, and hypertension) as key factors in the elevated risk of major metabolic or cardiovascular disease in MHO populations [41–43]. Thus, the buffering action of MHO on public healthcare expenditures in East Asia may only be as effective as the chosen interventions, which must address metabolic health through frequent monitoring of disease markers (such as high blood pressure or elevated triglycerides) and be maintained over a long time period to suppress transition.

With respect to prediabetes, there is currently controversy as to the impact of metabolically healthy obesity on its true effect. While MHO can be defined as “without type 2 diabetes”, chronically elevated glucose resulting from increasing insulin resistance can create elevated disease risk even without fully manifested diabetes [12]. Thus, proposals of HOMA-IR, the hyperinsulinemic-euglycemic clamp test, and other insulin homeostasis-specific evaluations are recommended to be incorporated as benchmarks to better indicate metabolic status since prediabetics can often register normal glucose values based on fasting time since feeding [11].

3.3. MHO to MUO Transition and Reversals in Eastern Asia

There is turnover in every obese population as some MHO sufferers transition into MUO status. While there is no globally applicable rate (due to variability in MHO definition), several studies have found eventual shifts from MHO into a metabolically unhealthy phenotype with increased cardiovascular, diabetes, and mortality risks. This was seen in a recent large study of 205,745 Taiwanese adults, which reported that 66.1% of MHO participants transitioned to MUO status within the 6-year mean follow-up period [44]. A similar 2019 report on the MESA (Multi-Ethnic Study of Atherosclerosis) survey found that over a 12.2-year median follow-up period, 48% of 1051 participants with MHO progressed to MUO and had increased cardiovascular disease risk [45]. This transition rate was mirrored by a 2019 report on the ATTICA study of 3042 adults that found a 52% transition rate from MHO to MUO over a 10-year period [46]. Importantly, the authors of the ATTICA report noted that insulin resistance and inflammatory status translated into significantly higher

cardiovascular disease risk over the 10-year study period [46]. This implies that a “stable” MHO status, desirable from a public health/healthcare cost savings standpoint, is reliant on biochemical factors that could potentially be controlled by diet, exercise, and other factors. Unfortunately, transitioning from MHO back to stable, normal weight status is rare, as a large 2020 study of 7,148,763 Korean adults found an MHO-to-metabolically-normal-and-normal-weight conversion rate of only 14.6% (252,858/7,148,763) [47]. MUO itself may be a point of no return, as type 2 diabetes is a chronic disease, and altered metabolisms may be highly resistant to even the newest drug therapies, requiring more invasive interventions.

4. Country-Level Analysis: China

4.1. Prevalence of Obesity-Related Diseases

A 2019 survey of 12,543 Chinese adults estimated the rate of obesity, defined by internal standards (23–26.9 kg/m² for overweight and 27.5 or greater kg/m² for obese), as 38.80% for overweight and 13.99% for obese status [48]. Even more troubling is the 43.15% prevalence of abdominal obesity (judged by waist circumference measurements of ≥ 90 cm for men and ≥ 80 cm for women), which is indicative of metabolic dysfunction induced by excess deposition of visceral fat and reflected in the global increases of obese persons in all Edmonton Obesity Staging System categories [48].

With respect to diabetes, a 2013–2018 survey by Wang et al. of 173,642 participants found a pre-diabetic prevalence of 38.1% and a type 2 diabetes prevalence of 12.4%, which was increased from 2013 (35.7% and 10.9%, respectively) [49]. Another survey by Li et al. in 2020 reported that from 2015 to 2017, prevalence rates of 35.2% for pre-diabetes, 12.8% for self-reported diabetes, and 6.0% for new cases of diabetes were discovered in a pool of 75,880 participants from 31 Chinese provinces [50]. Within these surveys, variability by region was noted, with northern (more rural) provinces suffering most and urban centers featuring better HbA1c control [50]. Obesity, blood pressure, red meat intake, poor exercise habits, heart rate, and blood lipids were positively associated with risk of pre-diabetes and diabetes pathogenesis in these surveys [49,50].

Cardiovascular diseases are climbing in China, as a meta-analysis of 15 national population survey reports ($n = 3,362,630$) found hypertension prevalence and control ranges of 18–44.7% and 4.2–30.1% [51]. The male gender, culturally associated with higher rates of smoking and alcohol consumption, was found to be positively associated with disease, and Chinese government guidelines for treatment in this population also emphasize the importance of glucose control and reductions in blood lipids [51]. Another survey in China conducted from 2012 to 2015 in a 451,755-person representative sampling group (representing 31 Chinese provinces) extrapolated data to estimate a hypertension prevalence of 23.2% of the adult population (~244.5 million) [52]. For heart failure and coronary heart disease (both related to obesity), a 50.0-million-person survey using national insurance information found a prevalence of 1.38% in adults older than 35, with 52.5% of afflicted patients having coronary heart disease [52].

4.2. Public Health Costs: Deaths

China's large and aging population is vulnerable to metabolic diseases precipitated from obesity rather than all-cause mortality, and higher BMI values have been strongly linked to cerebrovascular events and diabetes across the country [53,54]. This is due to the higher proportion of obese persons with comorbidities, especially hypertension and dyslipidemia [53]. A report that 5.09 million deaths in China were from cardiovascular disease in 2019, with stroke and ischemic heart disease comprising 87% of all cardiovascular-related deaths, attributed these deaths to hypertension, dyslipidemia, and hyperglycemia in addition to smoking [55]. Although lower in total than cardiovascular diseases, diabetes mortality is increasing in China, with increases of 38.5% (urban) and 254.9% (rural) in the age-adjusted death rates for diabetics during the period from 1989–2019 [56]. Of note is the rapid increase in age-adjusted mortality for urban and rural residents (10.0 to 12.7 and 3.4 to 9.4 per 100,000, respectively) as well as for both sexes in both urban and rural areas [56].

4.3. Public Health Costs: Funding

A recent survey of heart failure alone in China estimated a mean per-capita cost of USD 4407 for inpatients, and a 2012 estimation reported that heart failure total costs were USD 5.42 billion, indicating a severe burden on a country where even a 1.10% estimated prevalence translates into millions of patients [52,57]. A 2020 study on the direct costs of diabetes in management and subsequent heart, cerebral, and vascular diseases reported costs of USD 109 billion in 2019, increased care costs of up to USD 2847 per person during care for the first myocardial infarction, and a peak cost age range from 70 to 80 years old [58]. For obesity, a scoping meta-analysis of the time period from 2010–2020 found direct medical costs of between USD 8.4 and 23.9 billion but with additional indirect costs (facility, supply, record keeping, etc.) of up to USD 62.6 billion [59]. Thus, with expenditures on diabetes and obesity second only to the United States, China's health care system is under great strain from obesity and related issues of metabolic and cardio/cerebrovascular diseases.

4.4. Cause Analysis: China

Obesity has increased rapidly in China over the last 30 years, and studies have shown that caloric intake has almost doubled (1782 kcal/day in 1965 to 3200 kcal/day in 2018), with much of this increase coming from red meat and processed carbohydrates [60]. In spite of vitamin and mineral requirements meeting demand, the Chinese food supply is overly focused on processed foods and high-fat meats cooked in oil with relatively low calcium, as dairy consumption has not increased at the same rates as meat [60]. With regard to gender, although men are more likely to be obese, post-menopause is also strongly associated with increased obesity in Chinese women [53]. Smoking, a synergistic driver of obesity-related diseases, is another gender-specific concern in China, as a recent survey found that 52.9% of men smoke (compared to 2.4% of women), and only 23.6% of smokers intended to quit [61]. For alcohol consumption (a key driver of obesity, metabolic disorders, cardiovascular disease, and related complications), men were found to engage in more risky drinking behavior (43.2% vs. 9.3% in women) and consumed far more alcohol per week than women (4.0 vs. 1.2 drinks per week) even during COVID-19 quarantine measures [62].

Culture plays a strong role in Chinese obesity, as the One-Child Policy turned parental focus onto single children (most often boys) with expectations of academic achievement and "overcare", a phenomenon that has reduced physical activity and increased calorie consumption [63]. In a 2017 Chinese study, single children, especially in urban areas, were found to be at 4.5 times higher risk of developing obesity due to excess energy intake [63]. Additionally, recent memories of famine in grandparents, who are often tasked to care for children while both parents work, may result in overfeeding, a uniquely Chinese phenomenon [64]. For women, cultural pressure to be thin and avoid unladylike behaviors such as smoking and drinking may play a key role in the low smoking and drinking rates seen in reported studies. Thus, China's obesity crisis can be at least partially attributed to cultural, behavioral, and energy intake concerns.

Pollution is also a key concern of China. Due to its rapid industrialization, air pollution (ozone, particulate matter, and nitrogen species) is a significant issue in most urban areas, and several studies have found positive associations with pollution and overweight/obesity risk due to either exercise prevention or direct cardiovascular/pulmonary effects. A recent study found that particulate matter (<2.5 microns) and nitrogen dioxide were somewhat responsible for increased obesity risk in middle-aged or older men [65]. Conversely, green space has been positively associated with reduced risk of obesity in both children and adults [65,66].

Finally, thousands of years of famine pressure has selected numerous SNPs (47 or more) in diverse metabolism-associated genes that predispose the Chinese genotype to diabetes and obesity under conditions of higher calorie intake [67,68].

4.5. MHO Prevalence

China, with 1.4 billion people, stands to suffer if metabolically unhealthy obesity takes hold at rates traditionally seen in the West. A Chinese study of 4903 adult participants found an MHO prevalence of 20.0%, indicating that at least some of the overweight/obese adult population in China has MHO [69]. Another study of 22,376 adults (18 to 85) that used the International Diabetes Federation and WHO Asia-Pacific guidelines for diagnosis of metabolic disorders found an MHO prevalence of 15.2% in men and 5.3% in women [70]. Another survey of 13,525 mixed-ethnicity Chinese (Han, Kazakh, and Uyghur) adults found an MHO prevalence of 5.5% in this total population, but 38.5% of the obese participants were found to be of MHO status [71]. Thus, in China, the overall rate of MHO may be lower, but a significant portion of obese individuals may have MHO status and benefit from metabolically stabilizing interventions.

4.6. Potential Reductions in Death and Funding Costs with MHO

If China's MHO rate were increased by 10% (to around 30% of the obese), savings could be considerable, as even a temporary 10% reduction in obesity and related diseases could save up to USD 10 billion on diabetes, USD 840–2.39 billion on obesity itself, and USD 540 million on heart failure. Lowering mortality rates by 10% could save hundreds of thousands of lives. These possibilities would come from not only extending MHO status for the already obese, but reversions to MHO from MUO at even 10% could significantly reduce costs in both lives and public health care funding.

4.7. China-Specific Public Health Interventions

China's recommended interventions must be multidisciplinary and focus mainly on caloric intake, exercise, and culture. Education in healthy eating habits, especially in reviving the traditional Chinese diet focused on rice and vegetables, may be crucial in reducing obesity. A 2020 study on the Jiangnan (Yangtze-Delta-style) diet found that the lower prevalence of obesity in southern China versus high prevalence in northern China (as demarcated by the Qingling Mountain Range) comes from traditional reliance on whole grains, high-omega-6 rapeseed oil, fresh river fish, legumes, lower saturated fat/oil use, and lower salt intake, which is effectively a Chinese-style Mediterranean diet [72]. In contrast, processed wheat flour (bread), oil, high cooking temperature, refined oils, and meat consumption are much higher in northern China and are thought to be responsible for the higher rates of metabolic disease there [72]. Grandparents must also be educated to not overfeed children during childcare periods.

For exercise, relieving air pollution is a must, as is physical education and time for exercise. Other than the stereotypical image of the elderly doing Tai Chi in the park, actual levels of physical activity in Chinese children and adults do not meet the government-mandated guidelines, with only 15–34% of children meeting the amount and 11.9% of adults exercising in their leisure time [73,74].

Cultural changes, although the most difficult, would be of the greatest impact for China. Since social pressure on women to be thin and ladylike reduces their obesity, smoking, and drinking rates, group pressure is a very effective tactic against risky health behaviors in China. Social programs to discourage men from smoking, drinking, and gaining weight could be effective, but older men would need to lead this initiative, as the Confucian nature of Chinese society tends to value the older men as the example of behavior (filial piety), and these men can set the standards of harmonious Chinese society [75]. Additionally, socioeconomics plays a role in Chinese obesity, as a study of twins found that higher incomes and education are at least partially associated with less obesity even if caloric consumption does rise with income from poverty to middle-class levels [76].

China has recently joined the World Health Organization's World Obesity Day, with the National Health Commission of the People's Republic of China implementing vast programs to boost childhood nutrition education (e.g., Healthy Children Action Plan and

Sunshine Sports for Hundreds of Million Students) as well as the Three Reductions Plan and other programs to minimize the salt, oil, and sugar intake of all Chinese [77]. On a local level (province or smaller), these programs may be more effective if customized by province and combined with the above recommendations since governance within China is decentralized at the province level, while local governments have better success in running their own customized programs if corruption can be avoided [78,79]. The use of QR codes, tracking, and networking technology that were implemented during COVID-19 could be very effective in leveraging the local implementation of such vast public health initiatives [79]. The implementation of fiscal or other penalties for overweight/obese status, similar to the Japanese Metabo Law, may provide some reductions in obesity prevalence if counseling, medication, and treatment compliance measures are taken.

These changes may not completely arrest MUO but will serve to reduce waist circumference, restore glucose sensitivity, and at least extend MHO status or assist in converting from MUO to MHO status in the already obese.

5. Japan

5.1. Prevalence of Obesity-Related Diseases

A study of 55,229 adult Japanese employees from 2014 found that overweight/obese incidence rates were 28.3% and 6.7% in men compared to 14.3% and 3.9% for women [80]. This indicates that Japanese men are experiencing increased rates of overweight and obese statuses. However, these rates are far lower than China.

Diabetes rates in Japan are high and estimates vary, with a 2021 analysis of 10,917,173 observations from the national insurance database indicating a 2019 prevalence of 9.63% in men and 5.33% in women; these rates are up from an estimated 12.1% overall prevalence in 2016 [81,82]. Fatty liver parameters were also found to be the most closely associated with diabetes pathogenesis [81]. In contrast, a 2009 study found a national prevalence of 13.5%, but a large 2022 study of 2 million Japanese receiving public assistance found an average diabetes prevalence of 7.7%, with observed variability by region [83,84].

Hypertension remains a problem in Japan, even as the nationwide average systolic blood pressure has dropped from years 1961 to 2016 [85]. A 2020 study reported a hypertension prevalence of over 60% in men over 50 and post-menopausal women, with 43 million reported hypertensive patients in 2019; only 25% of these patients were considered in control of their condition [85,86]. Although a top performer in overall longevity, the observed decreases in ischemic heart disease (concurrent with declines in the total smoking population) have not similarly benefitted urban and middle-aged men, and disease in this group is more likely to consist of small-vessel blockages (arteriosclerosis) [87]. A 2013 analysis of six reports from 2000–2011 found heart disease rates in acute hospital admissions of 29.0–34.2% (age groups ranging from 40–75) but an overall rate of ~0.78% (~1,000,000/127,400,000) that was heavily influenced by hypertension and metabolic dysfunction [88]. In Japan, overall coronary heart disease death rates have fallen 61% during the 1980–2012 time period, and this was reported to be due to smoking cessation and improved systolic blood pressure control [89]. However, diabetes was considered a risk factor for heart disease in that study, and increased obesity with metabolic syndrome could offset improvements in cardiovascular morbidity and mortality rates [89]. This concept was bolstered by a recent report on the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-Japan) project, which found composite cardiovascular death risks (e.g., synergistic risks from co-morbidities such as obesity, diabetes, and hypertension) of up to 19.4% in men and 15.4% in women with two major risk factors over individual lifetimes [90].

5.2. Public Health Costs: Deaths

Japan, in spite of lower obesity rates, has not fully escaped mortality trends associated with metabolic diseases that are exacerbated by visceral fat. A large-scale study of 102,535 Japanese adults aged 40–79 years found that over 20 years, 4532 died from

cardiovascular disease (4.4%), and the risk of such deaths were 59% higher in the obese BMI category than for normal weight [91]. A similar large-scale analysis found that, of 79,457,000 adults aged 35–84, only 49,273 deaths in 2012 were attributable to heart disease; this rate is among the lowest in the world [89]. However, even though coronary heart disease mortality is predicted to further decrease from 2020 to 2040 (39,600 to 36,200 deaths in males vs. 27,400 to 23,600 in females), Japanese studies report that diabetes complications (e.g., nephropathy and macrovascular disease) contribute to higher all-cause mortality by leading to strokes instead of heart disease [92–94].

5.3. Public Health Costs: Funding

In spite of lower obesity rates, the costs to treat diabetes in Japan was estimated at 6% of the entire national healthcare budget in 2009, and this cost is expected to be the highest among developed nations by 2030 [83,84]. The estimated cost per patient for type 2 diabetes is around USD 4305 [95]. While heart disease prevalence is lower than other Asian countries, Japan still shoulders a large burden for heart failure care, with an estimated 2012–2014 cost of USD 1.187 billion and per-patient cost of USD 8089 [96]. Furthermore, the top 5% of serious cases accounted for 22% of this cost [96]. Since metabolic syndrome increases the risk of hypertension and subsequent serious heart diseases, type 2 diabetes is a high-cost chronic illness across all aspects of care for Japan's rapidly aging demographic [97,98]. Highly prevalent and poorly controlled (only 30–40% of patients have controlled high blood pressure), hypertension with its associated problems cost over USD 59 billion in medication and care for related stroke and heart disease in 2014 [99].

5.4. Cause Analysis: Japan

Although overall rates of obesity are less than elsewhere in Asia due to lower overall caloric intake, emphasis on soy/fish products, primary school lunch programs, occupational health initiatives, and lower animal protein intake, overweight/obesity rates are double in Japanese men compared to women, while youth, mostly due to increased sugar consumption, demonstrate significantly higher BMI values than older groups [80]. Such rising obesity, as a driver of hypertension and metabolic dysfunction, may thus be synergistic with the primary issues in Japan of hypertension and diabetes, driven by a high-salt traditional diet, lack of exercise, carbohydrate-heavy intake, and air pollution [100,101]. Although early treatment and lower salt intake have helped, Japan still faces regional issues with high concentrations of people affected by poorly controlled hypertension [101]. Furthermore, a genetic predisposition towards type 2 diabetes, with over 88 loci associated with adult-onset diabetes susceptibility, increases the risk of disease even at lower BMI and waist circumferences compared to Caucasians [102]. Expectations of working-age men to drink alcohol, smoke, and engage in after-work dinners with fatty, salty foods may be a sociocultural driver of obesity when paired with the excessive and mandatory overtime work (25–40+ hours overtime per month) endured by permanently employed workers in the sales and management departments of large companies and utility concerns [80,103]. Thus, a larger part of adult male obesity may be due to the social factors of heavy drinking, smoking, and poor diet associated with male-centric corporate life in Japan in contrast to the fat-negative social pressure on women [80].

5.5. MHO Prevalence

Japanese obesity prevalence has always been much lower than in the West, which translates into lower MHO prevalence compared to other countries. A survey of 802,288 participants in the Japan Medical Center Database indicated that over a 13-year sampling (until 2018), all obese participants were MHO, and this prevalence was 9.8% [42]. Since the rate of obesity is already very low in Japan (estimated at 6.7% for men, 3.9% for women), MHO may not be a significant factor in Japanese public health at the present [80].

5.6. Potential Reductions in Death and Funding Costs with MHO

As the MHO population is a small percentage of the total obese, which is also lower than other Asian countries, MHO would not be expected to create significant savings per obese patient in Japan. However, sustaining MHO in youth populations may prevent future MUO and associated costs.

5.7. Japan-Specific Public Health Interventions

Japan passed a controversial “Metabo Law” to formalize occupational health interventions in the overweight/obese middle-aged to elderly population. These interventions include education in weight loss, nutrition counseling, exercise instruction, and parameter tracking for participants. A 2018 analysis of 4,370,042 eligible participants over 3 years found significant reductions in all obesity-related areas, with concomitant reductions in cardiometabolic risk [104]. Coupled with an effective school lunch program supervised by nutritionists and sports/physical education in schools, Japan is already poised to combat unhealthy obesity and maximize chances to stop MUO progression [105].

Where Japan can improve is in lowering rates of smoking, especially in men, for whom smoking accounts for 27.8% of deaths [106]. With smoking rates of 38.2% in men and 11.6% in women, cessation and education are crucial to prevent this element from combining with obesity to drive cardiometabolic or cerebrovascular disease risk [106]. Another area of improvement is alcohol consumption, as heavy drinking habits were associated in a comprehensive study with single status, lower educational levels, smoking, and females working in large companies [107]. Reducing these co-factors will lessen the impact of any overweight/obese status on progression to diabetes and cardiometabolic risks. Unfortunately, other than warnings on tobacco products and alcohol containers, there are no large-scale anti-smoking or alcohol initiatives similar to the Metabo Law. Additionally, while smoking and alcohol cessation efforts (e.g., counseling) are covered under national insurance, it can be difficult to find treatment facilities (only 12% of registered facilities can provide such treatment), and there are no bans on cigarette or alcohol advertising [108]. The ideal implementation of anti-smoking and drinking programs at a national level would incorporate new technology such as smartphone apps with incentives as well as strong measures to separate the tobacco and alcohol industries from government ties previously instituted to derive reliable tax revenue from smoking and drinking [108]. Additionally, local-level programs would be ideal to capture the attention of those in the lower economic strata, for whom adverse health effects are generally more prevalent [109].

To combat diabetes, anti-pollution countermeasures, reductions in processed sugar consumption, and management of early-stage diabetes will both prevent and stabilize this potential obesogenic co-factor [110,111].

6. Comparisons and Contrasts from Country Analyses

Japan is representative of the power of collective effort to reduce obesity by legislation, and the low levels of obesity there are proof of the results. Chinese public health, in contrast, is at a more formative level and must reorient itself towards fighting obesity in youth, re-educating adults, and protecting the elderly from obesity-related diseases by action through its socialized healthcare system and efforts to increase exercise to stabilize metabolic health. However, Japan has not fully escaped from diseases (hypertension and diabetes) that can interact with obesity, even at low levels, to drive increased costs to the healthcare system. Thus, countries such as Japan should focus on anti-smoking, anti-alcohol, and stress reduction, while China should focus on exercise and calorie control through reversion to a traditional southern China diet. Once MUO rates stabilize or drop (due to reversion to MHO), China can then focus extensively on co-morbidity mitigation measures, similar to Japan.

7. Conclusions

East Asia is experiencing a surge in obesity that threatens both lives and public health funding. The progressive development of metabolic syndrome and obesity-related cardiovascular diseases in this population requires immediate action. The use of metabolically healthy obesity to stabilize public health could buffer mortality and healthcare expenditures in China, while the socialized medical system delays or reverses unstable obesity through cultural and educational measures. Japan, in contrast, can use similar methods to reduce the impact of obesity-associated co-morbidities on the overall health and cost within its adult and elderly population. Non-surgical and non-pharmacological interventions focused on unique sociocultural factors and deployed nationally through public health systems could thus be a cost-effective way to arrest the obesity pandemic.

Author Contributions: Conceptualization, figures, tables, and first draft, B.J.M.; design, revision, and approval, B.J.M., K.T. and Y.H. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. National Heart Lung and Blood Institute. *Managing Overweight and Obesity in Adults*; National Heart Lung and Blood Institute: Baltimore, MD, USA, 2013; p. 501. Available online: <https://www.nhlbi.nih.gov/sites/default/files/media/docs/obesity-evidence-review.pdf> (accessed on 3 January 2023).
2. Cawley, J.; Biener, A.; Meyerhoefer, C.; Ding, Y.; Zvenyach, T.; Smolarz, B.G.; Ramasamy, A. Direct medical costs of obesity in the United States and the most populous states. *J. Manag. Care Spec. Pharm.* **2021**, *27*, 354–366. [[CrossRef](#)] [[PubMed](#)]
3. Helble, M.; Francisco, K. *The Upcoming Obesity Crisis in Asia and the Pacific: First Cost Estimates*; Asian Development Bank Institute: Tokyo, Japan, 2017; p. 33. Available online: <https://www.adb.org/sites/default/files/publication/231516/adbi-wp679.pdf> (accessed on 3 January 2023).
4. Oku, A.; Ichimura, E.; Tsukamoto, M. Aging population in Asian Countries—Lessons from Japanese Experiences—PRI Discussion Paper Series. 2017. Available online: https://www.mof.go.jp/pri/research/discussion_paper/ron299.pdf (accessed on 3 January 2023).
5. Chen, R.; Xu, P.; Song, P.; Wang, M.; He, J. China has faster pace than Japan in population aging in next 25 years. *Biosci. Trends* **2019**, *13*, 287–291. [[CrossRef](#)] [[PubMed](#)]
6. Jang, I.-Y.; Lee, H.Y.; Lee, F. The 50th Anniversary Committee of Korean Geriatrics Society Geriatrics Fact Sheet in Korea 2018 from National Statistics. *Ann. Geriatr. Med. Res.* **2019**, *23*, 50–53. [[CrossRef](#)] [[PubMed](#)]
7. Zanella, M.T.; Kohlmann, O., Jr.; Ribeiro, A.B. Treatment of Obesity Hypertension and Diabetes Syndrome. *Hypertension* **2001**, *38*, 705–708. [[CrossRef](#)]
8. Nianogo, R.A.; Arah, O.A. Forecasting Obesity and Type 2 Diabetes Incidence and Burden: The ViLA-Obesity Simulation Model. *Front. Public Health* **2022**, *10*, 818816. [[CrossRef](#)]
9. Wondmkun, Y.T. Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications. *Diabetes Metab. Syndr. Obes. Targets Ther.* **2020**, *13*, 3611–3616. [[CrossRef](#)]
10. Li, W.; Fang, W.; Huang, Z.; Wang, X.; Cai, Z.; Chen, G.; Wu, W.; Chen, Z.; Wu, S.; Chen, Y. Association between age at onset of overweight and risk of hypertension across adulthood. *Heart* **2022**, *108*, 683–688. [[CrossRef](#)]
11. Smith, G.I.; Mittendorfer, B.; Klein, S. Metabolically healthy obesity: Facts and fantasies. *J. Clin. Investig.* **2019**, *129*, 3978–3989. [[CrossRef](#)]
12. Wu, J.D.; Liang, D.L.; Xie, Y. Prediabetes and risk of heart failure: The link grows stronger. *Cardiovasc. Diabetol.* **2021**, *20*, 112. [[CrossRef](#)]
13. Jiang, Y.; Li, Y.; Shi, K.; Wang, J.; Qian, W.-L.; Yan, W.-F.; Pang, T.; Yang, Z.-G. The additive effect of essential hypertension on coronary artery plaques in type 2 diabetes mellitus patients: A coronary computed tomography angiography study. *Cardiovasc. Diabetol.* **2022**, *21*, 1. [[CrossRef](#)]
14. Konwar, M.; Bose, D.; Jaiswal, S.K.; Maurya, M.K.; Ravi, R. Efficacy and Safety of Liraglutide 3.0 mg in Patients with Overweight and Obese with or without Diabetes: A Systematic Review and Meta-Analysis. *Int. J. Clin. Pract.* **2022**, *2022*, 1201977. [[CrossRef](#)]

15. Kritchevsky, S.B.; Beavers, K.M.; Miller, M.E.; Shea, M.K.; Houston, D.; Kitzman, D.W.; Nicklas, B.J. Intentional Weight Loss and All-Cause Mortality: A Meta-Analysis of Randomized Clinical Trials. *PLoS ONE* **2015**, *10*, e0121993. [CrossRef] [PubMed]
16. Kim, M.K.; Han, K.; Koh, E.S.; Kim, E.S.; Lee, M.-K.; Nam, G.E.; Kwon, H.-S. Weight change and mortality and cardiovascular outcomes in patients with new-onset diabetes mellitus: A nationwide cohort study. *Cardiovasc. Diabetol.* **2019**, *18*, 36. [CrossRef] [PubMed]
17. Xie, W.; Lundberg, D.J.; Collins, J.M.; Johnston, S.S.; Waggoner, J.R.; Hsiao, C.-W.; Preston, S.H.; Manson, J.E.; Stokes, A.C. Association of Weight Loss Between Early Adulthood and Midlife With All-Cause Mortality Risk in the US. *JAMA Netw. Open* **2020**, *3*, e2013448. [CrossRef] [PubMed]
18. Feldman, A.L.; Griffin, S.J.; Ahern, A.L.; Long, G.H.; Weinehall, L.; Fhärm, E.; Norberg, M.; Wennberg, P. Impact of weight maintenance and loss on diabetes risk and burden: A population-based study in 33,184 participants. *BMC Public Health* **2017**, *17*, 170. [CrossRef] [PubMed]
19. Targher, G.; Corey, K.E.; Byrne, C.D.; Roden, M. The complex link between NAFLD and type 2 diabetes mellitus—Mechanisms and treatments. *Nat. Rev. Gastroenterol. Hepatol.* **2021**, *18*, 599–612. [CrossRef]
20. Cohen, J.B. Hypertension in Obesity and the Impact of Weight Loss. *Curr. Cardiol. Rep.* **2017**, *19*, 98. [CrossRef]
21. LeBlanc, E.L.; Patnode, C.D.; Webber, E.M.; Redmond, N.; Rushkin, M.; O'Connor, E.A. *Behavioral and Pharmacotherapy Weight Loss Interventions to Prevent Obesity-Related Morbidity and Mortality in Adults: An Updated Systematic Review for the U.S. Preventive Services Task Force*; U.S. Preventive Services Task Force Evidence Syntheses, Formerly Systematic Evidence Reviews; Agency for Healthcare Research and Quality (US): Rockville, MD, USA, 2018.
22. Swaleh, R.; McGuckin, T.; Myroniuk, T.W.; Manca, D.; Lee, K.; Sharma, A.M.; Campbell-Scherer, D.; Yeung, R.O. Using the Edmonton Obesity Staging System in the real world: A feasibility study based on cross-sectional data. *CMAJ Open* **2021**, *9*, E1141–E1148. [CrossRef]
23. Ho-Pham, L.T.; Campbell, L.V.; Nguyen, T.V. More on body fat cutoff points. *Mayo Clin. Proc.* **2011**, *86*, 584–585. [CrossRef]
24. Goda, A.; Masuyama, T. Obesity and Overweight in Asian People. *Circ. J.* **2016**, *80*, 2425–2426. [CrossRef]
25. Ramachandran, A.; Chamukuttan, S.; Shetty, S.A.; Arun, N.; Susairaj, P. Obesity in Asia—Is it different from rest of the world. *Diabetes/Metab. Res. Rev.* **2012**, *28* (Suppl. S2), 47–51. [CrossRef] [PubMed]
26. Inoue, S.; Zimmet, P.; Caterson, I.; Chunming, C.; Ikeda, Y.; Khalid, A.; Kim, Y.S.; Bassett, J. The Asia—Pacific perspective: Redefining obesity and its treatment. *Int. Obes. Task Force* **2000**, *2*, 56.
27. Fyhofer, S. Report of the Council on Science and Public Health—Report 3-A-13. 2013. Available online: <https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/about-ama/councils/Council%20Reports/council-on-science-public-health/a13csaph3.pdf> (accessed on 3 January 2023).
28. Eurostat Statistics Explained. Overweight and Obesity—BMI Statistics. Available online: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Overweight_and_obesity_-_BMI_statistics (accessed on 3 January 2023).
29. April-Sanders, A.K.; Rodriguez, C.J. Metabolically Healthy Obesity Redefined. *JAMA Netw. Open* **2021**, *4*, e218860. [CrossRef]
30. Canning, K.L.; Brown, R.E.; Wharton, S.; Sharma, A.M.; Kuk, J.L. Edmonton Obesity Staging System Prevalence and Association with Weight Loss in a Publicly Funded Referral-Based Obesity Clinic. *J. Obes.* **2015**, *2015*, 619734. [CrossRef]
31. Blüher, M. Metabolically Healthy Obesity. *Endocr. Rev.* **2020**, *41*, bnaa004. [CrossRef]
32. Sharma, A.M.; Kushner, R.F. A proposed clinical staging system for obesity. *Int. J. Obes.* **2009**, *33*, 289–295. [CrossRef]
33. Mathis, B.J.; Tanaka, K.; Hiramatsu, Y. Factors of Obesity and Metabolically Healthy Obesity in Asia. *Medicina* **2022**, *58*, 1271. [CrossRef]
34. Liu, M.; Saredy, J.; Zhang, R.; Shao, Y.; Sun, Y.; Yang, W.Y.; Wang, J.; Liu, L.; Drummer, C.I.; Johnson, C.; et al. Approaching Inflammation Paradoxes—Proinflammatory Cytokine Blockages Induce Inflammatory Regulators. *Front. Immunol.* **2020**, *11*, 554301. [CrossRef]
35. McMurray, F.; Patten, D.A.; Harper, M.-E. Reactive Oxygen Species and Oxidative Stress in Obesity—Recent Findings and Empirical Approaches. *Obesity* **2016**, *24*, 2301–2310. [CrossRef] [PubMed]
36. Kim, D.H.; Sandoval, D.; Reed, J.A.; Matter, E.K.; Tolod, E.G.; Woods, S.C.; Seeley, R.J. The role of GM-CSF in adipose tissue inflammation. *Am. J. Physiol. Endocrinol. Metab.* **2008**, *295*, E1038–E1046. [CrossRef] [PubMed]
37. Wright, E., Jr.; Scism-Bacon, J.L.; Glass, L.C. Oxidative stress in type 2 diabetes: The role of fasting and postprandial glycaemia. *Int. J. Clin. Pract.* **2006**, *60*, 308–314. [CrossRef]
38. Safinowski, M.; Wilhelm, B.; Reimer, T.; Weise, A.; Thomé, N.; Hänel, H.; Forst, T.; Pfützner, A. Determination of nitrotyrosine concentrations in plasma samples of diabetes mellitus patients by four different immunoassays leads to contradictory results and disqualifies the majority of the tests. *Clin. Chem. Lab. Med.* **2009**, *47*, 483–488. [CrossRef]
39. Cobos-Palacios, L.; Ruiz-Moreno, M.I.; Vilches-Perez, A.; Vargas-Candela, A.; Muñoz-Úbeda, M.; Porres, J.B.; Navarro-Sanz, A.; Lopez-Carmona, M.D.; Sanz-Canovas, J.; Perez-Belmonte, L.M.; et al. Metabolically healthy obesity: Inflammatory biomarkers and adipokines in elderly population. *PLoS ONE* **2022**, *17*, e0265362. [CrossRef] [PubMed]
40. Zysk, B.; Ostrowska, L.; Smarkusz-Zarzecka, J. Salivary Adipokine and Cytokine Levels as Potential Markers for the Development of Obesity and Metabolic Disorders. *Int. J. Mol. Sci.* **2021**, *22*, 11703. [CrossRef] [PubMed]
41. Wang, B.; Zhang, M.; Wang, S.; Wang, C.; Wang, J.; Li, L.; Zhang, L.; Ren, Y.; Han, C.; Zhao, Y.; et al. Dynamic status of metabolically healthy overweight/obesity and metabolically unhealthy and normal weight and the risk of type 2 diabetes mellitus: A cohort study of a rural adult Chinese population. *Obes. Res. Clin. Pract.* **2018**, *12*, 61–71. [CrossRef]

42. Itoh, H.; Kaneko, H.; Kiriya, H.; Kamon, T.; Fujiu, K.; Morita, K.; Michihata, N.; Jo, T.; Takeda, N.; Morita, H.; et al. Metabolically Healthy Obesity and the Risk of Cardiovascular Disease in the General Population—Analysis of a Nationwide Epidemiological Database. *Circ. J.* **2021**, *85*, 914–920. [[CrossRef](#)]
43. Yeh, T.-L.; Hsu, H.-Y.; Tsai, M.-C.; Hsu, L.-Y.; Hwang, L.-C.; Chien, K.-L. Association between metabolically healthy obesity/overweight and cardiovascular disease risk: A representative cohort study in Taiwan. *PLoS ONE* **2021**, *16*, e0246378. [[CrossRef](#)] [[PubMed](#)]
44. Martinez-Gomez, D.; Ortega, F.B.; Hamer, M.; Lopez-Garcia, E.; Struijk, E.; Sadarangani, K.P.; Lavie, C.J.; Rodriguez-Artalejo, F. Physical Activity and Risk of Metabolic Phenotypes of Obesity: A Prospective Taiwanese Cohort Study in More Than 200,000 Adults. *Mayo Clin. Proc.* **2019**, *94*, 2209–2219. [[CrossRef](#)] [[PubMed](#)]
45. Mongraw-Chaffin, M.; Foster, M.C.; Anderson, C.A.; Burke, G.L.; Haq, N.; Kalyani, R.R.; Ouyang, P.; Sibley, C.T.; Tracy, R.; Woodward, M.; et al. Metabolically Healthy Obesity, Transition to Metabolic Syndrome, and Cardiovascular Risk. *J. Am. Coll. Cardiol.* **2018**, *71*, 1857–1865. [[CrossRef](#)]
46. Kouvari, M.; Panagiotakos, D.B.; Yannakoulia, M.; Georgousopoulou, E.; Critselis, E.; Chrysohoou, C.; Tousoulis, D.; Pitsavos, C.; ATTICA Study Investigators. Transition from meta-bolically benign to metabolically unhealthy obesity and 10-year cardiovascular disease incidence: The ATTICA cohort study. *Metabolism* **2019**, *93*, 18–24. [[CrossRef](#)]
47. Lee, Y.-B.; Kim, D.H.; Kim, S.M.; Kim, N.H.; Choi, K.M.; Baik, S.H.; Park, Y.G.; Han, K.; Yoo, H.J. Hospitalization for heart failure incidence according to the transition in metabolic health and obesity status: A nationwide population-based study. *Cardiovasc. Diabetol.* **2020**, *19*, 77. [[CrossRef](#)]
48. Chen, Y.; Peng, Q.; Yang, Y.; Zheng, S.; Wang, Y.; Lu, W. The prevalence and increasing trends of overweight, general obesity, and abdominal obesity among Chinese adults: A repeated cross-sectional study. *BMC Public Health* **2019**, *19*, 1293. [[CrossRef](#)] [[PubMed](#)]
49. Wang, L.; Peng, W.; Zhao, Z.; Zhang, M.; Shi, Z.; Song, Z.; Zhang, X.; Li, C.; Huang, Z.; Sun, X.; et al. Prevalence and Treatment of Diabetes in China, 2013–2018. *JAMA* **2021**, *326*, 2498. [[CrossRef](#)] [[PubMed](#)]
50. Li, Y.; Teng, D.; Shi, X.; Qin, G.; Qin, Y.; Quan, H.; Shi, B.; Sun, H.; Ba, J.; Chen, B.; et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: National cross sectional study. *BMJ* **2020**, *369*, m997. [[CrossRef](#)] [[PubMed](#)]
51. Yin, R.; Yin, L.; Li, L.; Silva-Nash, J.; Tan, J.; Pan, Z.; Zeng, J.; Yan, L.L. Hypertension in China: Burdens, guidelines and policy responses: A state-of-the-art review. *J. Hum. Hypertens.* **2022**, *36*, 126–134. [[CrossRef](#)]
52. Wang, Z.; Chen, Z.; Zhang, L.; Wang, X.; Hao, G.; Zhang, Z.; Shao, L.; Tian, Y.; Dong, Y.; Zheng, C.; et al. Status of Hypertension in China. *Circulation* **2018**, *137*, 2344–2356. [[CrossRef](#)]
53. Mu, L.; Liu, J.; Zhou, G.; Wu, C.; Chen, B.; Lu, Y.; Lu, J.; Yan, X.; Zhu, Z.; Nasir, K.; et al. Obesity Prevalence and Risks Among Chinese Adults: Findings From the China PEACE Million Persons Project, 2014–2018. *Circ. Cardiovasc. Qual. Outcomes* **2020**, *14*, e007292. [[CrossRef](#)]
54. Oakkar, E.E.; Stevens, J.; Truesdale, K.P.; Cai, J. BMI and all-cause mortality among Chinese and Caucasians: The People’s Republic of China and the Atherosclerosis Risk in Communities Studies. *Asia Pac. J. Clin. Nutr.* **2015**, *24*, 472–479. [[CrossRef](#)]
55. Liu, J.; Qi, J.; Yin, P.; Liu, Y.; You, J.; Lin, L.; Zhou, M.; Wang, L. Cardiovascular Disease Mortality—China, 2019. *China CDC Wkly.* **2021**, *3*, 323–326. [[CrossRef](#)]
56. Su, B.; Wang, Y.; Dong, Y.; Hu, G.; Xu, Y.; Peng, X.; Wang, Q.; Zheng, X. Trends in Diabetes Mortality in Urban and Rural China, 1987–2019: A Joinpoint Regression Analysis. *Front. Endocrinol.* **2022**, *12*, 777654. [[CrossRef](#)]
57. Yao, Y.; Zhang, R.; An, T.; Zhao, X.; Zhang, J. Cost-effectiveness of adding dapagliflozin to standard treatment for heart failure with reduced ejection fraction patients in China. *ESC Heart Fail.* **2020**, *7*, 3582–3592. [[CrossRef](#)]
58. He, X.; Zhang, Y.; Zhou, Y.; Dong, C.; Wu, J. Direct Medical Costs of Incident Complications in Patients Newly Diagnosed with Type 2 Diabetes in China. *Diabetes Ther.* **2021**, *12*, 275–288. [[CrossRef](#)]
59. Chen, Z.; Jiang, S.; Wang, Y.; Khan, M.M.; Zhang, D.; Rajbhandari-Thapa, J.; Li, L. Pharmacoeconomics of obesity in China: A scoping review. *Expert Rev. Pharmacoecon. Outcomes Res.* **2021**, *21*, 173–181. [[CrossRef](#)]
60. Liu, A.; Han, A.; Chai, L. Assessing the Nutrient Adequacy in China’s Food Supply from 1965 to 2018. *Nutrients* **2021**, *13*, 2734. [[CrossRef](#)] [[PubMed](#)]
61. Huang, X.; Fu, W.; Zhang, H.; Li, H.; Li, X.; Yang, Y.; Wang, F.; Gao, J.; Zheng, P.; Fu, H.; et al. Why are male Chinese smokers unwilling to quit? A multicentre cross-sectional study on smoking rationalisation and intention to quit. *BMJ Open* **2019**, *9*, e025285. [[CrossRef](#)]
62. Wang, Y.; Lu, H.; Hu, M.; Wu, S.; Chen, J.; Wang, L.; Luo, T.; Wu, Z.; Liu, Y.; Tang, J.; et al. Alcohol Consumption in China Before and During COVID-19: Preliminary Results From an Online Retrospective Survey. *Front. Psychiatry* **2020**, *11*, 597826. [[CrossRef](#)]
63. Min, J.; Xue, H.; Wang, V.H.; Li, M.; Wang, Y. Are single children more likely to be overweight or obese than those with siblings? The influence of China’s one-child policy on childhood obesity. *Prev. Med.* **2017**, *103*, 8–13. [[CrossRef](#)] [[PubMed](#)]
64. Liu, Y.; Zhao, J.; Zhong, H. Grandparental care and childhood obesity in China. *SSM-Popul. Health* **2022**, *17*, 101003. [[CrossRef](#)]
65. Chen, L.; Gao, D.; Ma, T.; Chen, M.; Li, Y.; Ma, Y.; Wen, B.; Jiang, J.; Wang, X.; Zhang, J.; et al. Could greenness modify the effects of physical activity and air pollutants on overweight and obesity among children and adolescents? *Sci. Total Environ.* **2022**, *832*, 155117. [[CrossRef](#)] [[PubMed](#)]

66. Han, W.; Xu, Z.; Hu, X.; Cao, R.; Wang, Y.; Jin, J.; Wang, J.; Yang, T.; Zeng, Q.; Huang, J.; et al. Air pollution, greenness and risk of overweight among middle-aged and older adults: A cohort study in China. *Environ. Res.* **2023**, *216 Pt 1*, 114372. [[CrossRef](#)] [[PubMed](#)]
67. Gong, W.; Li, H.; Song, C.; Yuan, F.; Ma, Y.; Chen, Z.; Wang, R.; Fang, H.; Liu, A. Effects of Gene-Environment Interaction on Obesity among Chinese Adults Born in the Early 1960s. *Genes* **2021**, *12*, 270. [[CrossRef](#)] [[PubMed](#)]
68. Ma, Z.; Wang, Y.; Xu, C.; Ai, F.; Huang, L.; Wang, J.; Peng, J.; Zhou, Y.; Yin, M.; Zhang, S.; et al. Obesity-Related Genetic Variants and Hyperuricemia Risk in Chinese Men. *Front. Endocrinol.* **2019**, *10*, 230. [[CrossRef](#)] [[PubMed](#)]
69. Yu, S.; Guo, X.; Li, G.X.; Yang, H.; Zheng, L.; Sun, Y. Metabolic healthy obesity is associated with higher incidence of mild decrease estimate glomerular rate in rural northeast Chinese. *BMC Nephrol.* **2020**, *21*, 505. [[CrossRef](#)]
70. Zhang, Y.; Fu, J.; Yang, S.; Yang, M.; Liu, A.; Wang, L.; Cao, S.; Sun, X.; Wang, F.; Liu, D. Prevalence of metabolically obese but normal weight (MONW) and metabolically healthy but obese (MHO) in Chinese Beijing urban subjects. *Biosci. Trends* **2017**, *11*, 418–426. [[CrossRef](#)] [[PubMed](#)]
71. Wang, W.Q.; Wei, B.; Song, Y.P.; Guo, H.; Zhang, X.H.; Wang, X.P.; Yan, Y.Z.; Ma, J.L.; Wang, K.; Keerman, M.; et al. Metabolically healthy obesity and unhealthy normal weight rural adults in Xinjiang: Prevalence and the associated factors. *BMC Public Health* **2021**, *21*, 1940. [[CrossRef](#)]
72. Wang, J.; Lin, X.; Bloomgarden, Z.T.; Ning, G. The Jiangnan diet, a healthy diet pattern for Chinese. *J. Diabetes* **2020**, *12*, 365–371. [[CrossRef](#)]
73. Chen, P.; Wang, D.; Shen, H.; Yu, L.; Gao, Q.; Mao, L.; Jiang, F.; Luo, Y.; Xie, M.; Zhang, Y.; et al. Physical activity and health in Chinese children and adolescents: Expert consensus statement (2020). *Br. J. Sports Med.* **2020**, *54*, 1321–1331. [[CrossRef](#)]
74. Li, C.; Wang, L.; Zhang, X.; Zhao, Z.; Huang, Z.; Zhou, M.; Wu, J.; Zhang, M. Leisure-Time Physical Activity Among Chinese Adults—China, 2015. *China CDC Wkly.* **2020**, *2*, 671–677. [[CrossRef](#)]
75. Nie, J.-B. The summit of a moral pilgrimage: Confucianism on healthy ageing and social eldercare. *Nurs. Ethics* **2021**, *28*, 316–326. [[CrossRef](#)]
76. Zheng, K.; Gao, W.; Cao, W.; Lv, J.; Yu, C.; Wang, S.; Huang, T.; Sun, D.; Liao, C.; Pang, Y.; et al. Education, income, and obesity: A nationwide Chinese twin study. *Obesity* **2022**, *30*, 931–942. [[CrossRef](#)]
77. Peng, W.; Zhang, J.; Zhou, H.; Zhang, A.; Wang, Y.; Tian, X.; Wen, D.; Wang, Y. Obesity intervention efforts in China and the 2022 World Obesity Day. *Glob. Health J.* **2022**, *6*, 118–121. [[CrossRef](#)]
78. Bardhan, P. The Chinese governance system: Its strengths and weaknesses in a comparative development perspective. *China Econ. Rev.* **2020**, *61*, 101430. [[CrossRef](#)]
79. Mei, C. Policy style, consistency and the effectiveness of the policy mix in China’s fight against COVID-19. *Policy Soc.* **2020**, *39*, 309–325. [[CrossRef](#)]
80. Hasegawa, M.; Akter, S.; Hu, H.; Kashino, I.; Kuwahara, K.; Okazaki, H.; Sasaki, N.; Ogasawara, T.; Eguchi, M.; Kochi, T.; et al. Five-year cumulative incidence of overweight and obesity, and longitudinal change in body mass index in Japanese workers: The Japan Epidemiology Collaboration on Occupational Health Study. *J. Occup. Health* **2020**, *62*, e12095. [[CrossRef](#)]
81. Kazumitsu, N. Estimation of Diabetes Prevalence, and Evaluation of Factors Affecting Blood Glucose Levels and Use of Medications in Japan. *Health* **2021**, *13*, 1431–1451.
82. Urakami, T.; Kuwabara, R.; Yoshida, K. Economic Impact of Diabetes in Japan. *Curr. Diabetes Rep.* **2019**, *19*, 2. [[CrossRef](#)]
83. Neville, S.E.; Boye, K.S.; Montgomery, W.S.; Iwamoto, K.; Okamura, M.; Hayes, R.P. Diabetes in Japan: A review of disease burden and approaches to treatment. *Diabetes/Metab. Res. Rev.* **2009**, *25*, 705–716. [[CrossRef](#)]
84. Sengoku, T.; Ishizaki, T.; Goto, Y.; Iwao, T.; Ohtera, S.; Sakai, M.; Kato, G.; Nakayama, T.; Takahashi, Y. Prevalence of type 2 diabetes by age, sex and geographical area among two million public assistance recipients in Japan: A cross-sectional study using a nationally representative claims database. *J. Epidemiol. Commun. Health* **2022**, *76*, 391–397. [[CrossRef](#)] [[PubMed](#)]
85. Hisamatsu, T.; Segawa, H.; Kadota, A.; Ohkubo, T.; Arima, H.; Miura, K. Epidemiology of hypertension in Japan: Beyond the new 2019 Japanese guidelines. *Hypertens. Res.* **2020**, *43*, 1344–1351. [[CrossRef](#)] [[PubMed](#)]
86. Hirawa, N.; Umemura, S.; Ito, S. Viewpoint on Guidelines for Treatment of Hypertension in Japan. *Circ. Res.* **2019**, *124*, 981–983. [[CrossRef](#)]
87. Iso, H. Cardiovascular disease, a major global burden: Epidemiology of stroke and ischemic heart disease in Japan. *Glob. Health Med.* **2021**, *3*, 358–364. [[CrossRef](#)]
88. Sakata, Y.; Shimokawa, H. Epidemiology of Heart Failure in Asia. *Circ. J.* **2013**, *77*, 2209–2217. [[CrossRef](#)]
89. Ogata, S.; Nishimura, K.; Guzman-Castillo, M.; Sumita, Y.; Nakai, M.; Nakao, Y.M.; Nishi, N.; Noguchi, T.; Sekikawa, A.; Saito, Y.; et al. Explaining the decline in coronary heart disease mortality rates in Japan: Contributions of changes in risk factors and evidence-based treatments between 1980 and 2012. *Int. J. Cardiol.* **2019**, *291*, 183–188. [[CrossRef](#)]
90. Imai, Y.; Tanaka, S.M.; Satoh, M.; Hirata, T.; Murakami, Y.; Miura, K.; Waki, T.; Hirata, A.; Sairenchi, T.; Irie, F.; et al. Prediction of Lifetime Risk of Cardiovascular Disease Deaths Stratified by Sex in the Japanese Population. *J. Am. Heart Assoc.* **2021**, *10*, 021753. [[CrossRef](#)]
91. Matsunaga, M.; Yatsuya, H.; Iso, H.; Li, Y.; Yamagishi, K.; Tanabe, N.; Wada, Y.; Ota, A.; Tamakoshi, K.; Tamakoshi, A. Impact of Body Mass Index on Obesity-Related Cancer and Cardiovascular Disease Mortality; The Japan Collaborative Cohort Study. *J. Atheroscler. Thromb.* **2022**, *29*, 1547–1562. [[CrossRef](#)]

92. Kiyoshige, E.; Ogata, S.; O’Flaherty, M.; Capewell, S.; Takegami, M.; Iihara, K.; Kypridemos, C.; Nishimura, K. Projections of future coronary heart disease and stroke mortality in Japan until 2040: A Bayesian age-period-cohort analysis. *Lancet Reg. Health-West. Pac.* **2022**, *31*, 100637. [[CrossRef](#)]
93. Yokomichi, H.; Nagai, A.; Hirata, M.; Mochizuki, M.; Kojima, R.; Yamagata, Z.; Project, B.J. Cause-specific mortality rates in patients with diabetes according to comorbid macro- and microvascular complications: BioBank Japan Cohort. *Endocrinol. Diabetes Metab.* **2021**, *4*, e00181. [[CrossRef](#)] [[PubMed](#)]
94. Islam, Z.; Akter, S.; Inoue, Y.; Hu, H.; Kuwahara, K.; Nakagawa, T.; Honda, T.; Yamamoto, S.; Okazaki, H.; Miyamoto, T.; et al. Prediabetes, Diabetes, and the Risk of All-Cause and Cause-Specific Mortality in a Japanese Working Population: Japan Epidemiology Collaboration on Occupational Health Study. *Diabetes Care* **2021**, *44*, 757–764. [[CrossRef](#)] [[PubMed](#)]
95. Ishii, H.; Madin-Warburton, M.; Strizek, A.; Thornton-Jones, L.; Suzuki, S. The cost-effectiveness of dulaglutide versus insulin glargine for the treatment of type 2 diabetes mellitus in Japan. *J. Med. Econ.* **2018**, *21*, 488–496. [[CrossRef](#)] [[PubMed](#)]
96. Kanaoka, K.; Okayama, S.; Nakai, M.; Sumita, Y.; Nishimura, K.; Kawakami, R.; Okura, H.; Miyamoto, Y.; Yasuda, S.; Tsutsui, H.; et al. Hospitalization Costs for Patients With Acute Congestive Heart Failure in Japan. *Circ. J.* **2019**, *83*, 1025–1031. [[CrossRef](#)] [[PubMed](#)]
97. Fujihara, K.; Sone, H. Cardiovascular Disease in Japanese Patients with Type 2 Diabetes Mellitus. *Ann. Vasc. Dis.* **2018**, *11*, 2–14. [[CrossRef](#)]
98. Tatsumi, Y.; Ohkubo, T. Hypertension with diabetes mellitus: Significance from an epidemiological perspective for Japanese. *Hypertens. Res.* **2017**, *40*, 795–806. [[CrossRef](#)]
99. Okada, H.; Johnston, K.; Nakayama, T.; Marra, C.; Tsuyuki, R.T. Economic Evaluation of Pharmacists Tackling the Burden of Hypertension in Japan. *Hypertension* **2019**, *74*, e54–e55. [[CrossRef](#)]
100. Lee, M.; Ohde, S. PM2.5 and Diabetes in the Japanese Population. *Int. J. Environ. Res. Public Health* **2021**, *18*, 6653. [[CrossRef](#)]
101. Sata, M.; Okamura, T.; Nishi, N.; Kadota, A.; Nakamura, M.; Kondo, K.; Okami, Y.; Kitaoka, K.; Ojima, T.; Yoshita, K.; et al. Trends in Prevalence, Treatment, and Control of Hypertension According to 40-Year-Old Life Expectancy at Prefectures in Japan from the National Health and Nutrition Surveys. *Nutrients* **2022**, *14*, 1219. [[CrossRef](#)] [[PubMed](#)]
102. Suzuki, K.; Akiyama, M.; Ishigaki, K.; Kanai, M.; Hosoe, J.; Shojima, N.; Hozawa, A.; Kadota, A.; Kuriki, K.; Naito, M.; et al. Identification of 28 new susceptibility loci for type 2 diabetes in the Japanese population. *Nat. Genet.* **2019**, *51*, 379–386. [[CrossRef](#)] [[PubMed](#)]
103. Kikuchi, H.; Odagiri, Y.; Ohya, Y.; Nakanishi, Y.; Shimomitsu, T.; Theorell, T.; Inoue, S. Association of overtime work hours with various stress responses in 59,021 Japanese workers: Retrospective cross-sectional study. *PLoS ONE* **2020**, *15*, e0229506. [[CrossRef](#)] [[PubMed](#)]
104. Nakao, Y.M.; Miyamoto, Y.; Ueshima, K.; Nakao, K.; Nakai, M.; Nishimura, K.; Yasuno, S.; Hosoda, K.; Ogawa, Y.; Itoh, H.; et al. Effectiveness of nationwide screening and lifestyle intervention for abdominal obesity and cardiometabolic risks in Japan: The metabolic syndrome and comprehensive lifestyle intervention study on nationwide database in Japan (MetS ACTION-J study). *PLoS ONE* **2018**, *13*, e0190862. [[CrossRef](#)] [[PubMed](#)]
105. Maruyama, S.; Kurokawa, A. The Operation of School Lunches in Japan: Construction of a System Considering Sustainability. *Jpn. J. Nutr. Diet.* **2018**, *76*, S12–S22. [[CrossRef](#)]
106. Akter, S.; Nakagawa, T.; Honda, T.; Yamamoto, S.; Kuwahara, K.; Okazaki, H.; Hu, H.; Imai, T.; Nishihara, A.; Miyamoto, T.; et al. Smoking, Smoking Cessation, and Risk of Mortality in a Japanese Working Population—Japan Epidemiology Collaboration on Occupational Health Study. *Circ. J.* **2018**, *82*, 3005–3012. [[CrossRef](#)] [[PubMed](#)]
107. Okui, T. An analysis of predictors for heavy alcohol drinking using nationally representative survey data in Japan. *BMC Public Health* **2021**, *21*, 359. [[CrossRef](#)] [[PubMed](#)]
108. Nagasawa, T.; Saito, J.; Odawara, M.; Imamura, H.; Kaji, Y.; Yuwaki, K.; Nogi, K.; Nakamura, M.; Shimazu, T. Smoking cessation interventions and implementations in Japan: A study protocol for a scoping review and supplemental survey. *BMJ Open* **2022**, *12*, e063912. [[CrossRef](#)] [[PubMed](#)]
109. Murakami, K.; Hashimoto, H. Associations of education and income with heavy drinking and problem drinking among men: Evidence from a population-based study in Japan. *BMC Public Health* **2019**, *19*, 420. [[CrossRef](#)] [[PubMed](#)]
110. Ni, L.; Yuan, C.; Chen, G.; Zhang, C.; Wu, X. SGLT2i: Beyond the glucose-lowering effect. *Cardiovasc. Diabetol.* **2020**, *19*, 98. [[CrossRef](#)]
111. Takahara, M.; Mita, T.; Katakami, N.; Wada, F.; Morita, N.; Kidani, Y.; Yajima, T.; Shimomura, I.; Watada, H. Three-Year Glycaemic Control and Management in Patients with Type 2 Diabetes Initiating Second-Line Treatment in Japan: A Prospective Observational Study, J-DISCOVER. *Diabetes Ther.* **2022**, *13*, 251–264. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.