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An update on physical health and economic consequences of overweight and obesity

Dinh-Toi Chu[1,2,†,*], Nguyen Thi Minh Nguyet[2,†], Thien Chu Dinh[3,†], Nguyen Vu Thai Lien[4], Khanh-Hoang Nguyen[5], Vo Truong Nhu Ngoc[4], Yang Tao[6], Le Hoang Son[7], Duc-Hau Le[8], Vu Bich Nga[9], Adam Jurgoński[10], Quoc-Hung Tran[11], Pham Van Tu[12], and Van-Huy Pham[13,*]

[1.]Faculty of Biology, Hanoi National University of Education, Hanoi, Vietnam

[3.] Centre for Molecular Medicine Norway (NCMM), Nordic EMBL Partnership, University of Oslo and Oslo University Hospital, Norway

[3.]Institute for Research and Development, Duy Tan University, K7/25 Quang Trung, Danang, Vietnam

[4.] Hanoi Medical University, Hanoi, Vietnam

[5.] School of Geography, Earth and Environmental Sciences, University of Birmingham, Birmingham, B15 2TT, United Kingdom

[6.] Nanjing Agricultural University, Nanjing 8 210095, China

[7.] VNU University of Science, Vietnam National University, Hanoi, Vietnam

[8.] VINMEC Research Institute of Stem Cell and Gene Technology, Hanoi, Vietnam

[9.] National Institute of Diabetes and Metabolic Disorders, Hanoi, Vietnam

[10.] Department of Biological Function of Food, Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, Tuwima 10 Str., 10-748 Olsztyn, Poland

[11.] University of Economics and Business, Vietnam National University, Hanoi, Vietnam

[12.] Faculty of Social Work, Hanoi National University of Education, Hanoi, Vietnam

[13.] Faculty of Information Technology, Ton Duc Thang University, Ho Chi Minh City, Vietnam

[†]Co-first authors

*Corresponding authors: To DTC: *chudinhtoi.hnue@gmail.com or dinhtc@ncmm.uio.no*

Or to VHP: *phamvanhuy@tdt.edu.vn*

Abstract

Overweight and obesity (OW and OB) have been on the increase globally and posed health risks to the world's population of all ages, including pre-born babies, children, adolescents, adults and elderly people, via their comorbid conditions. Excellent examples of comorbidities associated with obesity include cancer, cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2DM). In this article, we aimed to review and update scientific evidence regarding the relationships between obesity and its common physical health consequences, including CVD, T2DM, hypertension, ischemic stroke, cancer, dyslipidemia and reproductive disorders. In addition, the economic burden of OW and OB will be discussed. Abundant evidence is found to support the associations between obesity and other diseases. In general, the odd ratios, risk ratios or hazard ratios are often higher in OW and OB people than in the normal-weight ones. However, the molecular mechanism of how OW and OB induce the development of other diseases has not been fully understood. Figures also showed that obesity and its-related disorders exert enormous pressure on the economy which is projected to increase. This review highlights the fact that obesity can lead to numerous lethal health problems; therefore, it requires a lot of economic resources to fight against this epidemic.

Running title: Physical health and economic consequences of overweight and obesity

Keywords: Obesity; overweight; metabolic disorder; physical health consequences; economic burden

1. Introduction

Overweight and obesity are *"abnormal or excessive fat accumulation that may impair health"* and characterized by Body Mass Index (BMI) [1]. According to WHO, BMI <18.50 kg/m2 is defined as underweight, from 18.50 to <24.90 kg/m2 is considered as normal weight, ⩾ 25-29.9 kg/m^2 is defined as overweight or pre-obesity, and ⩾30 kg/m^2 is classified as obesity [2]. To measure nutritional status in children, however, age is taken into consideration. Overweight or obese under-5-year-old children have their weight-for-height greater than the median of Child Growth Standards (Created by WHO) plus 2 or 3 standard deviations (SD). Meanwhile, children aged 5-19 years whose BMI exceeds the median of WHO Growth Reference plus 1 SD are

classified as overweight, as opposed to 2 SD in case of obese children [1]. For Asian populations, an overweight person has a BMI range of 23 to less than 27.5 kg/m2 and an obese one has a BMI of at least 27 kg/m2 [3].

OW and OB are considered as one of the top health problems worldwide with approximately 2.8 million dead cases per annum [4, 5] and causing nearly 35.8 million disability adjusted life years (DALYs) [5]. According to WHO's updated data in 2017, obesity has experienced a 3-fold increase over the past four decades (1975-2016) [1]. In 2016, over 1.9 billion adults worldwide at the age of at least 18 years suffered from overweight, of whom more than 650 million were diagnosed with obesity (39% vs 13% of the global population, respectively). In 2016, 41 million under-5-year-old children, and >340 million 5-19-year-old children and adolescents were overweight and obese. In 1975, obese 5-19 year-olds of both sexes constituted only <1%, which then rose to 6% in females and 8% in males in 2016 [6]. Regarding age, children have a lower prevalence of obesity but higher rate of increase in obesity than adults [7].

The fastest rate of increase in obesity is predicted to occur in developing countries [8]. Developing countries experienced a greater increase in OW and OB prevalence than developed ones over the past two decades [9]. It was not until the early 1980-1990s when socioeconomic and nutritional conditions has improved that obesity came into existence as a big public health issue in economically developing countries [10]. Although most childhood OW and OB are recorded in developing countries, the percentage of overweight and obese children in these countries (6.1%) were just over half of that in developed ones (11.7%) [9]. Upper middle-income countries had an obesity prevalence of 24% more than triple the figure in lower middle-income countries (7%). While the figure for women from high income nations resembled that in men, obese women in other countries accounted for a dominant percentage. For example, women doubled the number of men with obesity in low to lower middle-income countries [5]. Furthermore, prevalence of OW and OB in children in poor countries increased at a rate 30% faster than in higher-income ones [11].

WHO's report in 2008 stated that overweight prevalence varied across the WHO Regions, from a low of 14% in South-East Asia (SEAR) to a concerning high of 62% in the Region of the

Americas (AMR), whereas the figure for obesity ranged between 3% in SEAR and 26% in AMR [5]. In terms of obesity, women outnumbered men in all of the six WHO Regions [5, 12]. As predicted by the Organization for Economic Co-operation and Development (OECD), obesity prevalence was projected to increase in nations like England, Mexico, USA, Italy, Korea, France, Spain and Switzerland in 2030 (between 9% and 47% of the population) [13].

2. Physical health consequences of obesity

Several health consequences are related to OW and OB such as CVD, hypertension (high blood pressure - HBP), ischemic, different types of cancer, T2DM, dyslipidaemia and reproductive conditions [14-19].

Cardiovascular diseases

Cardiovascular diseases are found more common among overweight and obese people and the risk of coronary heart disease (CHD) in obese patients is higher than that in healthy ones [20]. Alan J. Flint et al. found that the CHD risk in obese men (BMI>30 kg/m^2) was 1.81 times higher than in normal-weight men (18.5≤ BMI≤22.9 kg/m^2), compared to 2.16 times in the female group. Men with a waist circumference (WC) larger than 102.0 cm had a 2.2-fold higher risk of obesity than those with a 84-cm WC, while women with a 88-cm WC were 2.75 times higher at obesity risk than those having a 84-cm WC [21]. However, P. Dingli et al. suggested that the ratio of waist/hip, not BMI, be a predictor of acute myocardial infarction, or also known as heart attack [22]. According to Canoy D et al., if a women's BMI increased by 5 kg/m^2, she was 1.23 times more likely to become a new CHD case. Besides, there is a correlation between CHD incidence and BMI, CHD mortality in women with BMI<20 kg/m^2 and at least 35 kg/m^2 was 1.27 times and 2.84 times higher than those with BMI from 20 to 35 kg/m^2. For incident cases, the relative ratios (RRs) were 0.89 and 1.85, respectively [23]. Anne B. Gregory et al. found that people with raised BMI had higher prevalence of cardiac risk factors that normal ones. However, no association between BMI and cardiac-specific mortality after confounding factors were adjusted [24].

Strokes

Research has identified associations between strokes and obesity. Song YM et al found that elevated BMI was strongly associated to ischemic stroke risk in Korean men (aged 40 to 64; n=234,863) with age-adjusted hazard (HR) increased by 10% for each kg/m^2 increase in BMI [25]. Similarly, a significant increase in total and ischemic stroke was observed in American women (aged 45 years or above; n=39,876) compared to normal ones, women with obesity (BMI $\geqslant$30 kg/m^2) were at a higher risk of total stroke (HR = 1.5) and ischemic stroke (HR = 1.72) [26]. According to Zhou W et al., the stroke risk in Chinese individuals with upper-body fat distribution and those with high fat accumulation was double that among those with normal fat accumulation [27]. By analyzing 25 studies, Strazzullo P. et al. concluded that the risk of ischemic stroke among overweight people (RR=1.22) and obese participants was higher than normal-weight ones (RR 1.64) [28]. Recently, in a large scale study based in Israel with the participation of 2.3 million adolescents, the research group found that the mortality risk from adulthood stroke in participants with BMI $\geqslant$20 kg/m2 was higher than that in peoples with lower BMI. People with BMI $\geqslant$22.5 kg/m2 had higher risk of adulthood stroke-caused death than those with BMI from 17.5 to 19.9 kg/m2. Specifically, the HRs of stroke for participants increased with higher BMI [29].

Hypertension

According to an US study, obesity was a better predictor of hypertension than of other cardiovascular diseases, such as heart attack and stroke [30]. Obesity was considered as the leading contributor to hypertension [31]. Kang, Y.S. explained that obesity contributes to hypertension as a result of the interaction between the adipose tissue's secretion of adipokines and the inflammation of microvascular and perivascular adipose tissue [32]. Individuals with higher BMI have higher cardiac outputs, increase glomerular filtration rates [33], and their kidneys retains more sodium, leading to hypertension [34]. Several other mechanisms explain how obesity acts as a contributor of hypertension, such as insulin resistance, inflammation, and that neuropeptides (e.g. leptin), which possibly link obesity to the development of hypertension [35].

Research has shown that obesity increases a person's risk of hypertension. People with OW and OB were more likely to suffer from hypertension than ones with normal-weight [30, 36-

39]. Obese women are more prone to hypertension than obese men. The ratios were higher in women with higher BMI, while this association was not observed in men [40]. Both abdominal and central obesity contributed to hypertension in children [41]. A study in China and another in Poland concluded that hypertension among obese children was more common than non-obese ones [41, 42]. Besides, both types of blood pressure (systolic and diastolic) had positive associations with BMI [41, 42]

Weight gain contributes to increased blood pressure, both systolic and diastolic, thereby accelerating the risk of CHD and stroke [38, 43]. On the contrary, when overweight patients lost weight following low-calorie diet and consuming less sodium, their systolic and diastolic blood pressure levels both decreased considerably, as concluded by Reisin E and Frohlich ED [38, 44]. Weight loss can also be obtained by bariatric surgery - a weight loss-induced surgical procedure. According to Onyewu et al. hypertension was no longer found in 45% of patients who underwent bariatric surgery [45]. These weight loss interventions, therefore, are often used for hypertensive patients.

Type 2 Diabetes Mellitus (T2DM)

Obese people are more susceptible to T2DM than those with normal weight. The risk of T2DM in obese patients varied across studies [36, 46]. Central obesity, but not general obesity, was a predictor of T2DM [47]. Waist-to-hip ratio played a better role than WC and BMI in predicting T2DM, and both general and abdominal obesity were positively associated with pre-diabetes and T2DM[48]. Obese and abdominal obese people of all ages, including children and adolescents [49], middle-aged men [39], and elderly people [50], a seemed to suffer from diabetes than non-obese counterparts. While adults with obesity either during childhood or adulthood were not at risk of diabetes, the occurrence of obesity either in childhood alone or in both childhood and adulthood increased a person's risk of diabetes in his or her adulthood [49]. In terms of gender, males with general and abdominal obesity had higher likelihood of developing diabetes than females [50].

Some studies showed that obesity and gestational diabetes mellitus (GDM) have a two-way interaction. With a high pre-pregnancy BMI and obesity, women were more prone to GDM

[51], because insulin resistance and pre-diabetes were more commonly found in overweight and obese ones [52]. Mothers with GDM are a prediction for high BMI and obesity risk in their male children. However, there saw no strong correlation between obesity in female children and maternal GDM [53].

Cancer

As obesity is a contributor to millions cases of cancer worldwide with an annual incidence of about 85,000 obesity-related cancer patients in the USA alone, the relation between obesity and cancer has become a great concern worldwide [54]. Furthermore, one investigation has shown every increase of 5 kg/m^2 in BMI resulting in an increase of 10% in cancer mortality [54].

Raised BMI caused biogenic substances, including growth and sex hormones as well as inflammation-induced cytokines [55], to be produced over-abundantly, subsequently makes cells divide uncontrollably, leading to the formation of various types of cancer [5, 55]. Although the exact mechanism of how obesity causes cancer has been incompletely elucidated, the risk of cancer was proved to be associated to raised BMI [56].

Breast cancer is one the most common metastatic tumors and a death-leading cancer in women globally [57-59]. A study in India [60] and two Consortiums [61, 62] showed that BMI was a strong predictor of this cancer in women. In other words, individuals with OW and OBhad more potential to incur breast cancer than ones with normal-weight [60]. Increased BMI predicted the higher risk of ovarian cancer; high-grade invasive serous cancer was not attributed to obesity [61]. However, another study pointed out a strong association between the high-grade serous subtype of ovarian cancer with obesity, but it was not statistically significant [62]. The relationship between prostate cancer and obesity is also mentioned [63, 64], and low-grade prostate cancer was at a higher risk in obese patients [63]. A study in the Netherlands showed that both male and female patients were more at risk of all obesity-related cancers combined as BMI increased. Males with higher BMI were more prone to non-sex-specific cancers while female patients were more susceptible to sex-specific ones. Prostate cancer had no association with the increased BMI [64].

Dyslipidaemia

The association between dyslipidaemia and obesity has long been identified. In 1998, Martins J. et al. observed dyslipidaemia being common among mild to moderate obese woman [65]. In a study of 13,770 2-17 year –old-Chinese-children Li Y. et al. found that the odds of prevalent dyslipidaemia was 1.76 times higher in overweight than average-weight ones. The OR of having this condition in stunted overweight children was even higher, at 2.59 times [66]. When compared to average-weight Jordanian people, overweight and obese ones were also reported to have greater odds of having components of dyslipidaemia such as increase in triglyceride and total cholesterol, but reduction in high-density lipoprotein cholesterol) [67]. Similarly, some other studies also pointed out positive associations between evaluated BMI and dyslipidaemia prevalence in Vietnamese children [16], American Indian children and adolescents [68], middle-aged Iranians [69], or Chinese adults [70] . However, there remains controversial about whether obesity is an independent contributor to dyslipidaemia. For instance, dyslipidaemia was observed in certain unhealthy normal-weight individuals, but not found among the metabolically healthy ones with obesity [71, 72]. Ipsen et al. proposed that dyslipidaemia may be the risk factor of metabolic diseases rather than obesity [72]. Therefore, further studies about body weight and dyslipidaemia prevalence are needed for better understanding the mechanism underlying development of these two phenotypes.

Reproductive disorders

Psycho-physiologically, overweight or obesity is said to alter sexual function in both sexes [73-76]. BMI was found to have a significant correlation to sexual function in studies on Italian women [74, 77] and Iranian women [78]. However, obesity, but not overweight, increased the risk of erectile dysfunction in Chinese men over 40 years old [73]. French overweight or obese men had erectile dysfunction odd ratios of 2.69 or 2.58 in comparison with normal weight men, respectively [75].

OW and OB not only alter sexual function but also disrupt reproductive function in human. In children, obesity may delay puberty in boys and advance puberty in girls, but exactly how obesity affects puberty development is still unknown [79]. Some plausible mechanism of these

phenotypes are: central activation of gonadotropin-releasing hormone and gonadotropin secretion, obesity-related insulin resistance and hyperandrogenemia in girls; and increased aromatization of androgens to estrogens in boys [79]. Obesity has shown associations to subfertility and infertility in both men and women [80, 81]. By studying the level of anti-mullerian hormone (AMH), which helps predict the ovary's capacity of producing healthy eggs for fertilization, in 35-47-year-old women, Freeman E. et al. reported lower AMH concentrations in higher BMI women [82]. In other words, ovarian aging was faster in obese than normal weight women. Spontaneous pregnancy probability was lower in obese women in that every 1 kg/m^2 increase reduced the pregnancy rate by 4% [83]. For men, OW and OB were associated with genital tract inflammation (which consequently leads to infertility) and poor semen quality, or induced oxidative stress in testis [84-86].

3. Economic burden of overweight and obesity

The burden of this metabolic disorder is undeniably immense. Seidell JC categorized the burden into three groups, namely direct costs, societal or indirect costs, and personal costs. The first group covers medical costs for treating obesity and its related diseases [87].

The direct cost has seen an upward trend and it varies by country. In 2008, each overweight or obese individual in the USA spent $266 and $1,723 on healthcare, respectively. The combined cost of OW and OB amounted to $113.9 billion, accounting for 5-10% of the total national healthcare expenditure [88]. In 2010, $2,646 was spent on a male person with obesity, compared to $4,879 on a female person with obesity [89]. Medical costs per year in the USA are projected to increase to $66 billion by 2030 [90].

The economic burden of OW and OB in some other countries, including Hong Kong, China, Korea and Brazil, was lower than that in the USA. In 2011, Brazil's obesity-related direct costs amounted to about US $0.27 billion [91]. The medical costs at public hospitals in Hong Kong increased from US$ 0.29 to 0.43 billion in the period of1998 to 2002, consuming nearly 10% of the national healthcare expenditure in the public sector [92].

The costs of OW and OB -related diseases vary by country. In Brazil, the total healthcare costs for all OW and OB-associated diseases totaled US$ 2.1 billion [93]. In 2003, W. Zhao et al.

reported that in China the direct costs of OW and OB -related diseases, in ascending order, were US$ 0.97 billion (diabetes), 2.58 billion (CHD), 3.12 billion (hypertension) and 4.08 billion (strokes) [94]. A Korean study on people aged at least 20 years estimated the total OW and OB -related direct costs at about US$1.08 billion, including US $0.27 billion for inpatient care and US$0.30 million for outpatient care. In male patients, the costs for inpatient care due to ischaemic heart disease accounted for the highest part of seven types of inpatient costs. HBP contributed most significantly to the costs of either outpatient care or pharmaceuticals, irrespective of sex. The OW and OB -related cost of pharmaceuticals was > US $1 billion [95]. A study in English stated that the cost of 10 obesity-associated tumors in 2012-2013 was high (£0.32 billion). If the mean BMI gained 5kg/m2, it would experience a rise to £0.41 billion, and noticeably, the cost of uterus cancer alone would witness would increase most significantly, by 62% [96].

Societal or indirect expense refers to the value of lost work. Obese people perform less productively at work due to their absence from work, physical limitations, low life expectancy (premature deaths), disability pensions and unemployment benefits [87]. The Korean study estimated the OW and OB -related indirect cost to be US$ 706 million; the figure in men was nearly three times higher than that in women. Regardless of sex, the indirect cost for diabetes mellitus was highest. Productivity loss due to low life expectancy and hospitalization was calculated to be nearly US$ 444 million and US$ 74 million, respectively. Besides, the costs of time, transportation and nursing care were U$ 70 million, U$ 103 million and U$ 16 million [95].

Finally, in terms of personal costs, obese people are often stigmatized and discriminated at work due to their weight, obesity and related conditions, making their income lower than non-obese people. Due to poor health status, obese employees are charged with higher premiums and healthcare costs [87]. According to Thompson et al. healthcare cost for treating five obesity-related disorders, namely high cholesterol, hypertension, diabetes, stroke, and coronary artery disease, in OW and OB people was at least US$ 4,400 higher than that in normal-weight ones, irrespective of sex. Besides, the healthcare cost for men surpassed that for women in all categories of evaluated BMI [39].

Obesity has been on the increase worldwide and occurring in all ages and gender, especially in the young generations. It not only causes disease burdens but also contributes to direct, indirect and personal costs.

4. Conclusion

Many studies have proved the associations between obesity and life-threatening conditions, including CVD, cardio-metabolic disorders, T2DM, cancer and reproductive disorders (Fig. 1). The prevalence of some obesity-related diseases varies by gender and age of obesity onset. However, the exact molecular mechanisms of how obesity leads to the onset of other diseases are still unclear. In addition, OW and OB have also placed a massive burden on both economy and healthcare systems (Fig. 1). This review highlights the need for further study of the mechanisms of interaction between ill health conditions and excess body fat. Such knowledge is crucial to provide effective prevention of obesity and its-related diseases.

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Ethical statement

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest

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Figure 1. Physical health and economic consequences of overweight and obesity