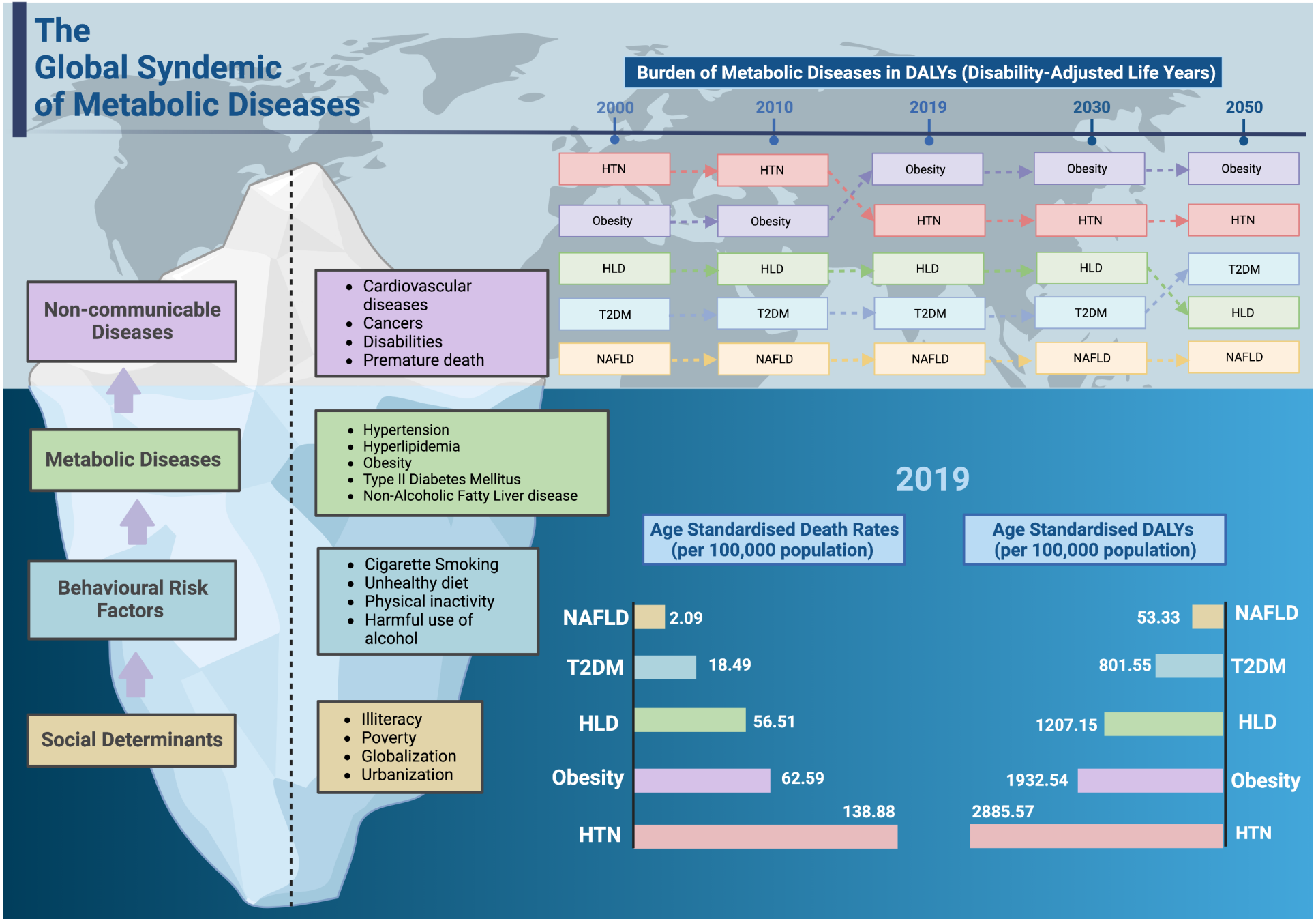

The Global Syndemic of Metabolic Diseases in the Young Adult Population: A Consortium of Trends and Projections from the Global Burden of Disease 2000-2019

Bryan Chong*[1] MBBS, Gwyneth Kong*[1] MBBS, Kannan Shankar*[1] MBBS, HS Jocelyn Chew[2] PhD, Chaoxing Lin[1] MBBS, Rachel Goh[1] MBBS, Yip Han Chin[1] MBBS, Darren Jun Hao Tan[1] MBBS, Kai En Chan[1] MBBS, Wen Hui Lim[1] MBBS, Nicholas Syn[1,2] MBBS, Siew Pang Chan[1,3,4] PhD, Jiong-Wei Wang[1,5] PhD, Chin Meng Khoo[1,6] MBBS, Georgios K Dimitriadis[7,8] MD, Karn Wijarnpreecha[9] MD, Arun Sanyal[10] MD, Mazen Noureddin[11] MD, Mohammad Shadab Siddiqui[12] MD, Roger Foo[1,4] MBBS, Anurag Mehta[13] MD, Gemma A Figtree[14,15] MBBS, Derek J Hausenloy[1,16,17,18,19] MBChB, Mark Y Chan[1,4] MBBS, Cheng Han Ng[1] MBBS, Mark Muthiah†[20,21] MBBS, Mamas A Mamas†[22,23] MBBCh, Nicholas WS Chew†[1,4] MBChB

[1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[2]Division of General Surgery, University Surgical Cluster, National University Hospital, Singapore, Singapore

[3]Department of Biostatistics, Cardiovascular Research Institute, National University Heart Centre (Singapore), NUHS

[4]Department of Cardiology, National University Heart Centre, National University Health System, Singapore

[5]Department of Surgery, Cardiovascular Research Institute (CVRI), National University Heart Centre Singapore

[6]Division of Endocrinology, Department of Medicine, National University Hospital, Singapore

[7]Department of Endocrinology ASO/EASO COM, King's College Hospital NHS Foundation Trust, Denmark Hill, London, United Kingdom

[8]Obesity, Type 2 Diabetes and Immunometabolism Research Group, Department of Diabetes, Faculty of Cardiovascular Medicine & Sciences, School of Life Course Sciences, King's College London, London, United Kingdom

[9]Division of Gastroenterology and Hepatology, University of Arizona College of Medicine Phoenix

[10]Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia, USA

[11]Houston Research Institute, Houston, Texas, USA

[12]Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia, USA

[13]Division of Cardiology, Virginia Commonwealth University, Richmond, Virginia

[14]Northern Clinical School, Kolling Institute of Medical Research, University of Sydney, Sydney, New South Wales, Australia

[15]Department of Cardiology, Royal North Shore Hospital, Sydney, New South Wales, Australia

[16]Cardiovascular & Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore

[17]National Heart Research Institute Singapore, National Heart Centre, Singapore

[18]The Hatter Cardiovascular Institute, University College London, London, UK

[19]Cardiovascular Research Center, College of Medical and Health Sciences, Asia University, Taiwan

[20]Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, Singapore, Singapore

[21]National University Centre for Organ Transplantation, National University Health System, Singapore

[22]Institute of Population Health, University of Manchester, Manchester, UK

[23]Keele Cardiac Research Group, Centre for Prognosis Research, Keele University, Stoke-on-Trent, UK

[†]These 3 authors supervised the work equally as senior authors.

*These 3 authors contributed equally as co-first authors.

Running title: Global burden of metabolic diseases in young adults

Address for Correspondence:

Dr Nicholas WS Chew

Department of Cardiology, National University Heart Centre

National University Health System, Singapore

5 Lower Kent Ridge Road, Singapore 119074

Email: nicholas_ws_chew@nuhs.edu.sg

Tel: (65) 6779 5555

Fax: (65) 6872 2998

ORCID-ID: 0000-0002-0640-0430

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Abbreviation list:

APC (Annual percentage change), DALYs (disability-adjusted life years), GBD (Global burden of diseases), HLD (hyperlipidemia), HTN (hypertension), ICD-10 (International Classification of Diseases-10), NAFLD (non-alcoholic fatty liver disease), NCDs (Non-communicable diseases), SDI (Socio-Demographic Index), T2DM (Type 2 diabetes mellitus), WHO (World Health Organisation), YLDs (years lived with disability)

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ABSTRACT

Background: A significant proportion of premature deaths globally are related to metabolic diseases in young adults. We examined the global trends and mortality of metabolic diseases in individuals aged below 40 years using data from the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) 2019.

Methods: From 2000-2019, global estimates of deaths and disability-adjusted life years (DALYs) were described for metabolic diseases (type 2 diabetes mellitus [T2DM], hyperlipidemia, hypertension, obesity, non-alcoholic fatty liver disease [NAFLD]). Subgroup analyses were performed based on sex, geographical regions and Socio-Demographic Index (SDI). Age-standardised death and DALYs were presented per 100,000 population with 95% uncertainty intervals (UI). Projections of mortality and DALYs were estimated using regression models based on the GBD 2019 data and combining them with Institute for Health Metrics and Evaluation projection counts for years up to 2050.

Results: In 2019, the highest age-standardised death rates were observed in hypertension (133·88 [121·25-155·73]), followed by obesity (62·59 [39·92-89·13]), hyperlipidemia (56·51 [41·83-73·62]), T2DM (18·49 [17·18-19·66]) and NAFLD (2·09 [1·61-2·60]). Similarly, obesity (1932·54 [1276·61-2639·74]) had the highest age-standardised DALYs, followed by hypertension (2885·57 [2580·75-3201·05]), hyperlipidemia (1207·15 [975·07-1461·11]), T2DM (801·55 [670·58-954·43]) and NAFLD (53·33 [40·73-68·29]). Mortality rates decreased over time in hyperlipidemia (-0·6%), hypertension (-0·47%), NAFLD (-0·31%) and T2DM (-0·20%), but not in obesity (1·07% increase). The highest metabolic-related mortality was observed in Eastern Mediterranean and low SDI countries. By 2050, obesity is projected to contribute to the largest number of deaths (102·8% increase from 2019), followed by hypertension (61·4% increase), hyperlipidemia (60·8% increase), T2DM (158·6% increase) and NAFLD (158·4% increase), with males continuing to bear the greatest burden across all metabolic diseases.

Conclusion: The growing burden of metabolic diseases, increasing obesity-related mortality trends, and the sex-regional-socioeconomic disparities evident in young adulthood, underlie the concerning growing global burden of metabolic diseases now and in future.

Abstract word count: 300

1. INTRODUCTION

Non-communicable diseases (NCDs) are the leading causes of morbidity and mortality worldwide [1], with estimates reported by the World Health Organisation (WHO) [2] to be over 15 million premature deaths attributed to NCDs annually [3]. A significant proportion of NCDs has been attributed to the rising burden of metabolic diseases; namely hypertension (HTN), type 2 diabetes mellitus (T2DM), hyperlipidaemia (HLD), obesity and more recently, non-alcoholic fatty liver disease (NAFLD) [4, 5]. These metabolic diseases are increasingly prevalent in the younger population, as modifiable lifestyles involving tobacco use, excess alcohol consumption, sedentary lifestyle and unhealthy diet are increasingly established in young adulthood, setting the stage for the development of metabolic diseases [2].

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) provides systematic estimates of the risk factors and causes of death worldwide, with stratification based on age, sex, location and socio-demographic index (SDI) [6] providing an opportunity to better understand the growing burden of metabolic diseases in young adults. Previous GBD studies have focused on the trends of each metabolic disease, with recent data beginning to emerge for young individuals [7, 8]. The present study provides unique perspectives on the global data estimates encompassing HTN, HLD, T2DM, obesity and NAFLD epidemics. This study examines the trends, burden and projections of metabolic diseases until 2050 using estimates from the GBD data, comparing them across sex, geographical regions and socio-economic status. The prevalence, age-standardised death rates, disability-adjusted life years (DALY) rates, and years lived with disability (YLDs), as well as future projections until 2050 will be reported to inform strategies for addressing metabolic diseases in the young adult population.

2. METHODS

2.1 Overview and Definition

Estimates from the GBD 2019 study, coordinated by the Institute for Health Metrics and Evaluation, were used for the analysis of trends in prevalence, DALYs and deaths of metabolic diseases and risk factors such as T2DM, HTN, HLD, obesity and NAFLD from the year 2000 to 2019. GBD 2019 is a multinational collaborative study across 204 countries and territories that is updated annually and designed to allow for consistent comparisons [9]. All data inputs can be obtained to generate estimates on the Global Health Data Exchange website [12]. We retrieved publication estimates of prevalence, deaths, DALYs, and YLDs for each metabolic disease, namely T2DM and NAFLD; and estimates of deaths, DALYs, and YLDs for HLD, HTN, and obesity, which were classified as metabolic risk factors rather than diseases in the GBD. Furthermore, as current clinical practice guidelines [13] recommend the evaluation of atherosclerotic cardiovascular disease risk in individuals aged 40 years and above, this study intends to examine the metabolic burden in younger adults who might be left undetected based on present risk stratification strategies [14]. As such, the GBD estimates were stratified to ages 15–39 years to obtain data on the metabolic diseases and risk factors in the younger adult population. Annual percentage change (APC) in rates was compared using a Joinpoint Regression Model to observe the trends in the metabolic diseases and risk factors over time when stratified by sex, location, and SDI. Aggregate prevalence, deaths, DALYs, and YLDs for each disease entity were obtained via International Classification of Diseases-10 (ICD-10) codes. Given the potential overlap of conditions in the same individual, we did not provide combined estimates of different metabolic diseases. The full details on the methods used to generate the GBD estimates have been described previously [15, 16] (Supplementary Material 1).

In terms of disease projections, historical data between 2000 and 2019 were tested for linear and quadratic trends. Based on visual inspection and evaluation of the models, we chose the most appropriate model with the best fit for each disease entity and population group. Using the predictions from the regression models and the Institute for Health Metrics and Evaluation projection [17] of population counts for years 2022–2050, we projected the burden of mortality and DALYs through to year 2050 for each metabolic disease entity. To examine the percentage change for each metabolic disease, the following equation was used:

$$Estimated\ percentage\ change$$

$$= \frac{(Estimates\ at\ the\ end\ of\ 5\ year\ period) - (Estimates\ at\ the\ start\ of\ 5\ year\ period)}{Estimates\ at\ the\ start\ of\ 5\ year\ period} \times 100\%.$$

The full details on the methods used to project GBD estimates have been described previously [18].

2.2 Death, DALYs, and YLDs Estimation in GBD 2019 Study

The primary outcome was mortality while secondary outcomes included prevalence, DALYs and YLDs. These estimates were retrieved through standardisation of input data and mapping of ICD-10 using methods of estimation employed by previous GBD studies [10, 11]. Age-standardised prevalence, death, DALY and YLD estimates were described with 95% uncertainty intervals (UIs), and the APC was presented with 95% confidence interval (CIs) of the age-standardised rates for the study period. An APC of 1% indicates a 1% increase per year while an APC of -0.5% indicates a 0.5% decrease per year.

2.3 Disease Prevalence, Socio-Demographic Index and World Health Organisation Regions

SDI was used as a composite measure of the average rankings of incomes per capita, average educational attainment and fertility rates [19] of the countries and territories [11]. This index is expressed on a scale of 0-1. An SDI of 0 indicates a theoretical minimum level of development relevant to health, while an SDI of 1 is the theoretical maximum and was used to classify the countries into high, high-middle, middle, low-middle, and low SDI countries. Data was stratified based on the WHO regions [20], namely Africa, Eastern Mediterranean, Europe, Region of Americas, South-East Asia, and Western Pacific. All statistical analysis was performed using Joinpoint Regression version 4.9.1.0 and STATA version 17.0.

3. RESULTS

3.1 Overview

In 2019, there was an estimated prevalence of 53.8 million and 425.8 million cases of T2DM and NAFLD respectively in young adults. The highest mortality was related to HTN with 219,545 deaths, followed by obesity with 182,167 deaths, HLD with 144,374 deaths, T2DM with 23,355 deaths, and NAFLD with 10,971 deaths. From 2000 to 2019, there were annual declines in age-standardised mortality rates for T2DM (-0.20%), HLD (-0.60%) , HTN (-0.47%) and NAFLD (-0.31%). In contrast, there was an annual increase of 1.07% in death rates for obesity (Figure 1A). Annual declines in age-standardised DALYs were observed for NAFLD (-0.33%), HTN (-0.32%), HLD (-0.55%); whereas there were annual increases for obesity (1.48%) and T2DM (1.35%) between 2000-2019 (Figure 1B). Similarly, there were annual increases in YLDs related to obesity and T2DM, but not in NAFLD, HTN, and HLD (Supplementary Figure 1). The largest proportion of mortality was observed in HTN (Figure 2A), whilst majority of metabolic-related DALYs and YLDs were related to obesity (Figure 2B, Supplementary Figure 2).

3.2 Type 2 Diabetes Mellitus

3.2.1 Global Prevalence

The age-standardised prevalence rate of young adults with T2DM in 2019 was 5,283 (95% UI 4,854 to 5,752) per 100,000 population. There was a 2.07% annual increase in T2DM-related prevalence from 2000 to 2019 (2.29% increase in males and 1.81% in females). Larger annual increase of T2DM prevalence was observed in countries with increasing SDI, from 1.32% in low SDI to 3.08% in high SDI countries (Supplementary Table 1).

3.2.2 Diabetes-Related Mortality

The age-standardised death rate in individuals with T2DM in 2019 was 18.49 (95% UI 17.18 to 19.66) per 100,000 population. T2DM-related mortality rates decreased (-0.20%) from 2000 to 2019. Significant annual reduction was observed in females (-0.44%) but not in males (Table 1).

3.2.3 Diabetes-Related Mortality Differences Based on Geographical Region and SDI

The change in T2DM-related mortality from 2000 to 2019 varied across geographical regions, with the largest reduction in South-East Asia (-1.03%), while the Eastern Mediterranean (1.59%) observed increased mortality rates (Supplementary Figure 3). In 2019, T2DM-related death rates were the highest in Africa (39.30 [95% UI 35.50 to 43.36]) and Eastern Mediterranean (32.26 [95% UI 28.22 to 36.22]); whilst Western Pacific (10.42 [95% UI 9.28 to 11.45]) and Europe (10.22 [95% UI 9.32 to 10.89]) had the lowest.

An estimated 22,260 deaths (95.3% of total deaths) related to T2DM occurred in low to high-middle SDI countries. T2DM-related death rate in 2019 was the lowest in high SDI (9.05 [95% UI 8.29 to 9.55]] and highest in low SDI countries (31.89 [95% UI 28.95 to 35.05]). From 2000 to 2019, reduction of T2DM-related death rates was only reported in high SDI (-0.83%) and high-middle SDI countries (-0.58%).

3.2.4 Diabetes-Related DALYs and YLDs

In 2019, there was an estimated 4.5 million T2DM-related DALYs, with an APC of 1.35% from 2000 to 2019. Males experienced a larger annual increase in DALYs (1.58%) than females (1.04%). There were 3.2 million YLDs related to T2DM, with an annual increase of 2.11% from 2000 to 2019.

3.3 Hypertension

3.3.1 Hypertension-Related Mortality

In 2019, the age-standardised death rate in individuals with HTN was 138.88 (95% UI 121.25 to 155.73) per 100,000 population. There was a decrease in HTN-related mortality rate from 2000 to 2019, with annual reduction of -0.47%; although significant reduction was observed only in females (-1.37%) (Table 2).

3.3.2 Hypertension-Related Mortality Differences Based on Geographical Region and SDI

In 2019, Eastern Mediterranean had the highest age-standardised death rates of 242.78 (95% UI 207.76 – 277.97) per 100,000 population. From 2000 to 2019, the largest decrease in HTN-related mortality rates was seen in South-East Asia (-1.14%), whilst the Eastern Mediterranean observed an annual increase of 0.81% (Supplementary Figure 4).

In 2019, an estimated 209,080 deaths (95.2% of total deaths) occurred in low to high-middle SDI countries. The age-standardised death rates of HTN were lowest at 69.76 (95% UI 58.67 to 79.66) in high SDI, and highest in low SDI countries at 169.85 (95% UI 147.99 to 191.20). There were decreases in HTN-related death rates from 2000 to 2019 in all countries, with the largest recorded in high-middle SDI countries.

3.3.3 HTN-Related DALYs and YLDs

In 2019, there were 13.9 million HTN-related DALYs, with an annual reduction of -0.32% from 2000 to 2019. This reduction in DALYs was only observed in females. YLDs related to HTN was estimated to be 1.7 million, with an annual increase of 1.06% over time.

3.4 Non-alcoholic Fatty Liver Disease

3.4.1 Prevalence of NAFLD

In 2019, the age-standardised prevalence rate of NAFLD was 15,023 (95% UI 13,494 to 16,765) per 100,000 population. The annual increase in NAFLD-related prevalence rates was 1.01%, with a larger increase in males (1.18%) than in females (0.81%). The age-standardised prevalence rates were highest in the Eastern Mediterranean region (24,762 [95% UI 22,600 to 27,110]) and lowest in Europe (12,502 [95% UI 11,260 to 13,832]). The Western Pacific (1.40%) observed the largest increase in prevalence rates from 2000 to 2019 (Supplementary Table 2).

3.4.2 NAFLD-Related Mortality

In 2019, the age-standardised death rate in individuals with NAFLD was 2.09 (95% UI 1.61 to 2.60) per 100,000 population. Between 2000–2019, the annual reduction in NAFLD-related death rate was -0.31%. This decrease was only significant in females (-0.73%) (Table 3).

3.4.3 NAFLD-Related Mortality Differences Based on Geographical Region and SDI

In 2019, NAFLD-related age-standardised death rates were the highest in Eastern Mediterranean (4.13 [95% UI 2.91 to 5.68]). There were increases in death rates for NAFLD from 2000 to 2019 in

Europe (2.39%) and Eastern Mediterranean (0.48%), but reductions in Western Pacific (-2.28%), South-East Asia (-0.85%), and Africa (-0.32%) (Supplementary Figure 5).

In 2019, 10,484 deaths (95.6% of total death) related to NAFLD occurred in low to high-middle SDI countries. The NAFLD-related age-standardised death rates generally decreased in countries with increasing SDI, with the lowest in high SDI (1.37 [95% UI 1.07 to 1.72]) and highest in low SDI countries (2.79 [95% UI 2.05 to 3.74]). From 2000 to 2019, the largest decrease in death rates was seen in the high SDI countries (-0.92%).

3.4.4 NAFLD-Related DALYs and YLDs

In 2019, 630,891 DALYs were estimated to be related to NAFLD, with annual reduction of -0.33% in DALYs from 2000 to 2019. This reduction was only significant in females (-0.74%). There were 7,435 YLDs related to NAFLD, with an annual increase of 0.38% over time.

3.5 Hyperlipidaemia

3.5.1 HLD-Related Mortality

In 2019, the HLD-related age-standardised death rate was 56.51 (95% UI 41.83 to 73.62) per 100,000 population. There was an annual reduction in HLD-related death rates of -0.60% from 2000 to 2019, which was more pronounced in females (-1.37%) than in males (-0.26%) (Table 4).

3.5.2 Hyperlipidemia-Related Mortality Differences Based on Geographical Region and SDI

Age-standardised death rate of HLD was highest in Eastern Mediterranean (110.64, 95% UI 82.10 to 142.21), and lowest in Region of Americas (40.44, 95% UI 30.00 to 52.53). From 2000 to 2019, the largest decrease in death rates was observed in Europe (-1.91%) (Supplementary Figure 6).

In 2019, 136,716 deaths (94.7% of all deaths) related to HLD occurred in low to high-middle SDI countries. The age-standardised death rate was lowest in high SDI countries (32.94 [95% UI 24.03 to 43.46]) and highest in high-middle SDI (70.67 [95% UI 51.79 to 93.69]). The largest decrease in the death rates from 2000 to 2019 was observed in high-middle (-1.37%) SDI countries.

3.5.3 Hyperlipidemia-Related DALYs and YLDs

In 2019, 8.5 million DALYs were estimated to be related to HLD, with an annual change of -0.55%. A larger reduction of DALYs was observed in females (-1.23%) than in males (-0.23%). Conversely, there were 603,592 YLDs related to HLD, with an annual increase (0.33%) from 2000 to 2019.

3.6 Obesity

3.6.1 Obesity-Related Mortality

The 2019 age-standardised death rate related to obesity was 62.59 (95% UI 39.92 to 89.13) per 100,000 population. From 2000 to 2019, death rates increased by 1.07% annually, with a larger increase in males (1.61%) than in females (0.22%). There was an estimated 15.2 million DALYs related to obesity in 2019, with 1.48% annual increase in DALY rates from 2000 to 2019 (Table 5).

3.6.2 Obesity-Related Mortality Differences Based on Geographical Region and SDI

The highest obesity-related age-standardised death rate in 2019 was seen in the Eastern Mediterranean region (130.97, 95% UI 87.38 to 179.78), and the lowest in Western Pacific (38.38, 95% UI 18.10 to 64.89). From 2000 to 2019, South-East Asia (1.76%) and Western Pacific (1.72%) regions reported the largest increases in obesity-related death rates; with only Europe (-0.56%) observing a decrease (Figure 3).

In 2019, 168,969 obesity-related deaths (92.8% of total deaths) occurred in low to high-middle SDI countries. The death rate was the lowest in the high SDI (46.65 [95% UI 29.76 to 63.76]), and the highest in the high-middle SDI countries (69.14 [95% UI 44.00 to 98.24]). Increase in obesity-related death rates from 2000 to 2019 was highest in low-middle SDI countries (2.11%), with no changes in death rates observed in high and high-middle SDI countries.

3.6.3 Obesity-Related DALYs and YLDs

In 2019, an estimated 15.2 million DALYs were related to obesity, with annual increase of 1.48% from 2000 to 2019. Males had larger increases in DALYs (1.91%) than females (0.95%). There were 5.0 million YLDs related to obesity, with annual increase of 2.50% from 2000 to 2019.

3.7 Projected Deaths and DALYs

By the year 2050, the largest burden of deaths is projected to be related to obesity with 369,492 deaths (102.8% increase from 2019), followed by HTN with 354,256 deaths (61.4% increase), HLD with 232,224 deaths (60.8% increase), T2DM with 60,405 deaths (158.6% increase), and NAFLD with 28,345 deaths (158.4% increase) (Figure 4; Supplementary Table 3). From 2019 to 2050, males will continue to bear the larger burden of deaths compared to females for all metabolic diseases (Supplementary Figure 7). However, females are projected to have a larger percentage increase in HTN and HLD-related deaths and DALYs (Supplementary Table 4).

The largest burden of DALYs, by the year 2050, will be found in obesity with 31.6 million DALYs (108.0% increase from 2019), followed by HTN with 22.3 million DALYs (61.6% increase), HLD with 13.9 million DALYs (64.3% increase), T2DM with 10.1 million DALYs (123.4% increase), and NAFLD with 1.6 million DALYs (153.8% increase) (Supplementary Table 5). The fastest increase in HTN, HLD, NAFLD, and obesity-related DALYs is projected to occur between years 2035 and 2040 (Figure 5). From 2019 to 2050, males will continue to have higher DALYs compared to females for all metabolic diseases.

4. DISCUSSION

Previous GBD studies depicted the young population's metabolic burden by examining each disease entity in silos. The main driver of incident chronic liver diseases amongst the young adult population has shifted from viral hepatitis to NAFLD [8], mirroring the rising obesity prevalence as elucidated by earlier GBD 2013 studies [21]. Moreover, the socioeconomic and geographical disparity in the incidence of metabolic diseases, such as diabetes [7], is already evident as early as young adulthood. However, as metabolic diseases share similar upstream pathomechanistic processes and underlying societal drivers, the present consortium adds to the present literature by consolidating the metabolic diseases under the umbrella concept of the 'Global Metabolic Syndemic' affecting the young adult population. This provides a valuable construct in comparing the trends of the metabolic components, as well as projecting the burden of metabolic diseases in the decades ahead (Graphical Abstract). The data portray the concerning findings of the growing burden of metabolic diseases and risk factors such as T2DM, HTN, HLD, obesity and NAFLD, which parallels the global shift in lifestyle practices that has already made its impact on our young adults. The rising disease burden over the past two decades, with obesity and HTN identified as the main drivers of the global burden of metabolic disease, allows stakeholders to implement effective strategies in targeting the entrenched contributors. The WHO estimates that 70% of worldwide premature deaths stem from behaviours begun in adolescence and young adulthood [22]. The study predicts that obesity will surpass HTN as the main contributor of metabolic disease-related deaths and DALYs in the years ahead. This offers a critical opportunity to inform important stakeholders in prioritising upstream solutions to tackle the silent obesity epidemic and curb the incidence of metabolic diseases globally, through effective interventions that address underlying social and economic precursors of metabolic risks in young adults. Unhealthy behaviours that perpetuate later into life often become challenging to modify, as reflected by the lack of success in sustained metabolic improvement with lifestyle interventions [23-26].

The putative biological underpinnings of the metabolic wave, dominated by the rising obesity epidemic, are complex and often share close and bidirectional associations with other metabolic disorders. Visceral obesity increases lipotoxicity, insulin resistance, pro-inflammatory mediators (such as interleukin-6, C-reactive protein) that can accelerate the metabolic sequalae [27, 28]. Although

metabolic diseases are often interdependent, recent evidence has suggested that each metabolic disorder may have independent associations with adverse cardiovascular prognosis. For instance, NAFLD increases the risk of chronic kidney disease, stroke [29, 30] and cardiovascular diseases [31], independent of T2DM and HTN. Nevertheless, the focus on metabolic health in the young adult population is critical in halting the downstream effects of disparate metabolic health that may persist across generations. Population-based studies have demonstrated that low and high birth weights are associated with deleterious long-term metabolic health, including obesity, fasting glucose impairment, HTN, NAFLD, hypertriglyceridemia, and HLD [32]. Societal drivers such as poorer education levels, especially in socioeconomically disadvantaged populations, were also reported to perpetuate the disparate birth weight within the population [32, 33].

Even though the disparity in mortality rates across sex, geographical and socioeconomic factors have been described in previous GBD studies [9], we highlight that this disparity begins as early as young adulthood across metabolic diseases. The most significant decreases in mortality for T2DM, HTN, HLD and NAFLD were observed in females, with the largest increase in obesity-related mortality seen in males. This sex disparity in favour of women is likely multifactorial, with biological advantages related to the protective effect of oestrogen on the risk of metabolic disease [34], as well as fat distribution and pattern of fat loss between both sexes [35]. This highlights the importance of developing targeted and sex-specific strategies when addressing metabolic diseases in the young population [24]. Moreover, the considerable variation in mortality across geographical regions, particularly with excess mortality predominantly in the Middle Eastern and African regions, may be contributed by the deeply entrenched social and cultural factors [36], as well as biological differences in fat patterning, body composition and cardiometabolic effects of a high body mass index [37]. In addition, there is a sense of urgency in tackling the disparate burden of metabolic diseases in the young population, given the paradoxical trends of the lower prevalence but higher mortality burden of disease in low SDI countries. This disparity is further exacerbated by the gradient of increasing prevalence yet lower mortality burden across the countries with increasing SDI quintile.

Despite the global efforts to tackle the rising epidemic of metabolic diseases [38], the unabated rise in the global prevalence of metabolic diseases over the past two decades is of concern. This consortium

projects the global burden of metabolic diseases that will be expected to continue to rise with worrisome trends. The projected increase in deaths and DALYs will disproportionately affect males more than females, but females are predicted to see a larger increase in the burden of HTN and HLD in the future. A particularly striking result is the dominance of obesity, surpassing HTN, as the main contributing disease for both deaths and DALYs in the future [39, 40]. Indeed young adults have been increasingly exposed to the obesogenic environment attributed to increased globalisation, interconnectivity, technological advancements, decreases in activity and the convenience of energy-rich foods [41]. The significant increases in obesity-related mortality and DALYs over the years draw concerns over the potential delayed disease progression of obesity to other metabolic manifestations [42, 43]. With increasing life expectancy, the global burden of metabolic diseases is bound to rise further if these shared metabolic drivers are not addressed effectively [44]. The projections from this study may serve as a motivator and help modify policy development in implementing preventive strategies with a more targeted sex-specific approach with emphasis on risk stratification and interventions focused on tackling the root causes of obesity and metabolic disease differences in the ever-changing populations [18]. Concerted efforts in addressing sex- and cultural-specific barriers and facilitators to weight management and health literacy are crucial in addressing the global disparity [45]. Similarly, pharmacological agents should target the reduction of the overall metabolic milieu rather than a disease in isolation [46]. Emerging evidence on the beneficial effects of glucagon-like peptide-1 receptor agonists (GLP1-RA) that help improve weight loss, reduce hepatic fat, glycemic levels and importantly, cardiovascular events [47], offer hope for future reduction in obesity-related mortality [48].

4.1 Strengths and Limitations

This study takes advantage of the 'Global Metabolic Syndemic' framework and compares the trends of all metabolic diseases in the young adult population, stratified based on sex, geographical regions and socioeconomic standing. The findings are essential in informing policymaking strategies with the projection of the global metabolic burden up to 2050. Moreover, the GBD 2019 study is one of the most comprehensive worldwide databases of diseases and has been utilised by various policy-makers globally to direct public health policy. The GBD has made several comprehensive efforts to ensure accurate GBD estimates, accountability, comparability of measurement, and generalisability

[49]. In our study, we have included the complete data estimates derived from the GBD 2019 study, thus allowing the findings to represent the broader populations [49]. However, this study is not without its limitations. First, the GBD data's reliability depends on the quality and availability of the individual country's vital registration system. However, in areas without data sources, GBD estimates rely on the modelling processes, predictive covariates and temporal trends derived from neighbouring countries that may lead to inherent biases [16]. Nevertheless, GBD has managed this issue over the years by reinforcing annual searches with in-country collaborators for available data, enforcing data cleaning, correction, and maximising data utility. Second, even though metabolic diseases often occur as a cluster of diseases and metabolic risk factors that collectively increases the risk of atherosclerotic cardiovascular diseases [4, 50-52], the lack of granularity in individual patient data within the database did not allow the examination of the synergistic or additive effects of the combination of metabolic diseases. As such, this study could only compare the trends of each metabolic component.

4.2 Future Directions

With the unified goal to reduce the burden of metabolic disease in future decades, the present study emphasises the importance of addressing the shared drivers of metabolic diseases from a young age [53]. To further future research that can have a significant impact on clinical decision-making, we propose the 'Global Metabolic Syndemic' framework, or the synergy of epidemics as described by the *Lancet* Obesity Commission [54], since these metabolic diseases often exist in tandem, share common pathomechanistic pathways and underlying societal drivers, that collectively contribute to the development of cardiovascular disease [55-59], disability, cancers, and premature deaths [7, 16]. Historically, each metabolic entity was considered in isolation, but consolidating the collective metabolic burden into a single global syndemic framework can help focus the attention on addressing the combined challenges and reminds us of the importance of prioritising standard upstream solutions in order to mitigate the overall metabolic milieu of the individual [4, 54]. Stakeholders can shift their attention to developing sex-, geographical- and socioeconomic-specific programs to enhance the screening, detection and prevention of metabolic diseases in young adults that have the potential benefit of reducing healthcare demands and spending.

The integration of population health and biomedical sciences through the strategic partnerships between researchers, clinicians and policymakers can facilitate the implementation of novel translational discoveries into clinical practice. With the pursuit of the first US Food and Drug Administration-approved NAFLD therapeutics in the pipeline, now being evaluated in late-stage clinical trials, future translational studies are warranted to explore the additional metabolic effects of these therapeutics (namely peroxisome proliferator-activated receptor agonists, GLP1-RA) on the overall metabolic milieu such as insulin sensitivity, de-novo lipogenesis, and weight reduction [25, 60]. The enthusiasm for discovering novel therapeutics and their benefits on metabolic health is ever-increasing but should maintain the importance of lifestyle modifications and optimisation of cardiovascular comorbidities.

5. Conclusion

The growing burden of metabolic diseases over the past two decades, accompanied by the increasing obesity-related mortality trends, presents a significant global burden of metabolic diseases now and in the years ahead. The disparities in the burden of metabolic diseases stem from entrenched sex-regional-socioeconomic precursors that begin as early as young adulthood. The focus on young people is paramount, and there is a sense of urgency in implementing effective preventative and therapeutic strategies at the individual, communal and national levels to derail the projected trajectory of the metabolic burden.

FIGURE LEGENDS

Graphical abstract. The 'Global Metabolic Syndemic' framework.

Figure 1. A) Number of deaths and age-standardised death rates and B) disability-adjusted life year (DALYs) and Age-standardised DALYs in individuals less than 40 years of age, at the global level by the five metabolic diseases, 2000-2019

Bar charts depict the total Deaths/DALYs and line graphs depict the age-standardised rates of Deaths/DALYs

Figure 2. A) Proportion of deaths and, B) Proportion of disability-adjusted life years (DALYs) due to the five metabolic diseases in individuals less than 40 years of age, at global and regional levels by sex, 2019

Figure 3. The global trends of a) age-standardised mortality and b) percentage change in obesity in individuals less than 40 years of age

Figure 4. Projection of Disease-adjusted Life Years (DALYs) by disease from 2020 to 2050

Figure 5. Bar graph of Percentage Change of Disability-adjusted Life Years (DALYs) by disease from 2020 to 2050

DATA SHARING

Data used in the analyses is publicly available, and can be found on the Global Health Data Exchange GBD 2019 website.

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CONFLICTS OF INTEREST

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AS is the President of Sanyal Biotechnology and has stock options in Genfit, Akarna, Tiziana, Indalo, Durect, and Galmed. He has served as a consultant to Astra Zeneca, Nitto Denko, Enyo, Ardelyx, Conatus, Nimbus, Amarin, Salix, Tobira, Takeda, Jannsen, Gilead, Terns, Birdrock, Merck, Valeant, Boehringer Ingelheim, Lilly, Hemoshear, Zafgen, Novartis, Novo Nordisk, Pfizer, Exhalenz, and Genfit. He has been an unpaid consultant to Intercept, Echosens, Immuron, Galectin, Fractyl, Syntlogic, Affimune, Chemomab, Zydus, Nordic Bioscience, Albireo, Prosciento, Surrozen, and Bristol Myers Squibb. His institution has received grant support from Gilead, Salix, Tobira, Bristol Myers Squibb, Shire, Intercept, Merck, Astra Zeneca, Malinckrodt, Cumberland, and Norvatis. He receives royalties from Elsevier and UptoDate.

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AUTHOR CONTRIBUTIONS

Bryan Chong: Methodology, Investigation, Data curation, Formal analysis, Writing - original draft, review & editing

Gwyneth Kong: Methodology, Investigation, Data curation

Kannan Shankar: Methodology, Investigation, Data curation, Formal analysis, Writing - original draft, review & editing

HS Jocelyn Chew: Data curation, Writing - review & editing

Chaoxing Lin: Investigation, Data curation, Formal analysis

Rachel Goh: Investigation, Data curation, Formal analysis

Yip Han Chin: Investigation, Data curation, Formal analysis

Darren Jun Hao Tan: Validation, Writing - review & editing

Kai En Chan: Validation, Writing - review & editing

Wen Hui Lim: Validation, Writing - review & editing

Nicholas Syn: Data curation, Writing - review & editing

Siew Pang Chan: Investigation, Data curation, Formal analysis

Jiong-Wei Wang: Supervision, Writing - review & editing

Chin Meng Khoo: Supervision, Writing - review & editing

Georgios Dimitriadis: Supervision, Writing - review & editing

Karn Wijarnpreecha: Supervision, Writing - review & editing

Arun Sanyal: Supervision, Writing - review & editing

Mazen Noureddin: Supervision, Validation Writing - review & editing

Mohammad Shadab Siddiqui: Supervision, Writing - review & editing

Roger Foo: Supervision, Writing - review & editing

Anurag Mehta Supervision, Writing - review & editing

Gemma Figtree: Supervision, Writing - review & editing

Derek Hausenloy: Supervision, Writing - review & editing

Mark Chan: Supervision, Validation, Writing - review & editing

Cheng Han Ng: Conceptualization, Supervision, Writing - review & editing

Mark Muthiah: Supervision, Writing - review & editing

Mamas A Mamas: Methodology, Data curation, Supervision, Validation, Writing - review & editing

Nicholas WS Chew: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Software, Supervision, Validation, Writing - original draft, review & editing

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The Global Syndemic of Metabolic Diseases in the Young Adult Population: A Consortium of Trends and Projections from the Global Burden of Disease 2000-2019

Bryan Chong*[1] MBBS, Gwyneth Kong*[1] MBBS, Kannan Shankar*[1] MBBS, HS Jocelyn Chew[2] PhD, Chaoxing Lin[1] MBBS, Rachel Goh[1] MBBS, Yip Han Chin[1] MBBS, Darren Jun Hao Tan[1] MBBS, Kai En Chan[1] MBBS, Wen Hui Lim[1] MBBS, Nicholas Syn[1,2] MBBS, Siew Pang Chan[1,3,4] PhD, Jiong-Wei Wang[1,5] PhD, Chin Meng Khoo[1,6] MBBS, Georgios K Dimitriadis[7,8] MD, Karn Wijarnpreecha[9] MD, Arun Sanyal[10] MD, Mazen Noureddin[11] MD, Mohammad Shadab Siddiqui[12] MD, Roger Foo[1,4] MBBS, Anurag Mehta[13] MD, Gemma A Figtree[14,15] MBBS, Derek J Hausenloy[1,16,17,18,19] MBChB, Mark Y Chan[1,4] MBBS, Cheng Han Ng[1] MBBS, Mark Muthiah†[20,21] MBBS, Mamas A Mamas†[22,23] MBBCh, Nicholas WS Chew†[1,4] MBChB

[1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[2]Division of General Surgery, University Surgical Cluster, National University Hospital, Singapore, Singapore

[3]Department of Biostatistics, Cardiovascular Research Institute, National University Heart Centre (Singapore), NUHS

[4]Department of Cardiology, National University Heart Centre, National University Health System, Singapore

[5]Department of Surgery, Cardiovascular Research Institute (CVRI), National University Heart Centre Singapore

[6]Division of Endocrinology, Department of Medicine, National University Hospital, Singapore

[7]Department of Endocrinology ASO/EASO COM, King's College Hospital NHS Foundation Trust, Denmark Hill, London, United Kingdom

[8]Obesity, Type 2 Diabetes and Immunometabolism Research Group, Department of Diabetes, Faculty of Cardiovascular Medicine & Sciences, School of Life Course Sciences, King's College London, London, United Kingdom

[9]Division of Gastroenterology and Hepatology, University of Arizona College of Medicine Phoenix

[10]Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia, USA

[11]Houston Research Institute, Houston, Texas, USA

[12]Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia, USA

[13]Division of Cardiology, Virginia Commonwealth University, Richmond, Virginia

[14]Northern Clinical School, Kolling Institute of Medical Research, University of Sydney, Sydney, New South Wales, Australia

[15]Department of Cardiology, Royal North Shore Hospital, Sydney, New South Wales, Australia

[16]Cardiovascular & Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore

[17]National Heart Research Institute Singapore, National Heart Centre, Singapore

[18]The Hatter Cardiovascular Institute, University College London, London, UK

[19]Cardiovascular Research Center, College of Medical and Health Sciences, Asia University, Taiwan

[20]Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, Singapore, Singapore

[21]National University Centre for Organ Transplantation, National University Health System, Singapore

[22]Institute of Population Health, University of Manchester, Manchester, UK

[23]Keele Cardiac Research Group, Centre for Prognosis Research, Keele University, Stoke-on-Trent, UK

[†]These 3 authors supervised the work equally as senior authors.

*These 3 authors contributed equally as co-first authors.

Running title: Global burden of metabolic diseases in young adults

Address for Correspondence:

Dr Nicholas WS Chew

Department of Cardiology, National University Heart Centre

National University Health System, Singapore

5 Lower Kent Ridge Road, Singapore 119074

Email: nicholas_ws_chew@nuhs.edu.sg

Tel: (65) 6779 5555

Fax: (65) 6872 2998

ORCID-ID: 0000-0002-0640-0430

Key words

Global burden; metabolic disease; hypertension; diabetes mellitus; non-alcoholic fatty liver disease

Abbreviation list:

APC (Annual percentage change), DALYs (disability-adjusted life years), GBD (Global burden of diseases), HLD (hyperlipidemia), HTN (hypertension), ICD-10 (International Classification of Diseases-10), NAFLD (non-alcoholic fatty liver disease), NCDs (Non-communicable diseases), SDI (Socio-Demographic Index), T2DM (Type 2 diabetes mellitus), WHO (World Health Organisation), YLDs (years lived with disability)

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ABSTRACT

Background: A significant proportion of premature deaths globally are related to metabolic diseases in young adults. We examined the global trends and mortality of metabolic diseases in individuals aged below 40 years using data from the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) 2019.

Methods: From 2000-2019, global estimates of deaths and disability-adjusted life years (DALYs) were described for metabolic diseases (type 2 diabetes mellitus [T2DM], hyperlipidemia, hypertension, obesity, non-alcoholic fatty liver disease [NAFLD]). Subgroup analyses were performed based on sex, geographical regions and Socio-Demographic Index (SDI). Age-standardised death and DALYs were presented per 100,000 population with 95% uncertainty intervals (UI). Projections of mortality and DALYs were estimated using regression models based on the GBD 2019 data and combining them with Institute for Health Metrics and Evaluation projection counts for years up to 2050.

Results: In 2019, the highest age-standardised death rates were observed in hypertension (133·88 [121·25-155·73]), followed by obesity (62·59 [39·92-89·13]), hyperlipidemia (56·51 [41·83-73·62]), T2DM (18·49 [17·18-19·66]) and NAFLD (2·09 [1·61-2·60]). Similarly, obesity (1932·54 [1276·61-2639·74]) had the highest age-standardised DALYs, followed by hypertension (2885·57 [2580·75-3201·05]), hyperlipidemia (1207·15 [975·07-1461·11]), T2DM (801·55 [670·58-954·43]) and NAFLD (53·33 [40·73-68·29]). Mortality rates decreased over time in hyperlipidemia (-0·6%), hypertension (-0·47%), NAFLD (-0·31%) and T2DM (-0·20%), but not in obesity (1·07% increase). The highest metabolic-related mortality was observed in Eastern Mediterranean and low SDI countries. By 2050, obesity is projected to contribute to the largest number of deaths (102·8% increase from 2019), followed by hypertension (61·4% increase), hyperlipidemia (60·8% increase), T2DM (158·6% increase) and NAFLD (158·4% increase), with males continuing to bear the greatest burden across all metabolic diseases.

Conclusion: The growing burden of metabolic diseases, increasing obesity-related mortality trends, and the sex-regional-socioeconomic disparities evident in young adulthood, underlie the concerning growing global burden of metabolic diseases now and in future.

Abstract word count: 300

1. INTRODUCTION

Non-communicable diseases (NCDs) are the leading causes of morbidity and mortality worldwide [1], with estimates reported by the World Health Organisation (WHO) [2] to be over 15 million premature deaths attributed to NCDs annually [3]. A significant proportion of NCDs has been attributed to the rising burden of metabolic diseases; namely hypertension (HTN), type 2 diabetes mellitus (T2DM), hyperlipidaemia (HLD), obesity and more recently, non-alcoholic fatty liver disease (NAFLD) [4, 5]. These metabolic diseases are increasingly prevalent in the younger population, as modifiable lifestyles involving tobacco use, excess alcohol consumption, sedentary lifestyle and unhealthy diet are increasingly established in young adulthood, setting the stage for the development of metabolic diseases [2].

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) provides systematic estimates of the risk factors and causes of death worldwide, with stratification based on age, sex, location and socio-demographic index (SDI) [6] providing an opportunity to better understand the growing burden of metabolic diseases in young adults. Previous GBD studies have focused on the trends of each metabolic disease, with recent data beginning to emerge for young individuals [7, 8]. The present study provides unique perspectives on the global data estimates encompassing HTN, HLD, T2DM, obesity and NAFLD epidemics. This study examines the trends, burden and projections of metabolic diseases until 2050 using estimates from the GBD data, comparing them across sex, geographical regions and socio-economic status. The prevalence, age-standardised death rates, disability-adjusted life years (DALY) rates, and years lived with disability (YLDs), as well as future projections until 2050 will be reported to inform strategies for addressing metabolic diseases in the young adult population.

2. METHODS

2.1 Overview and Definition

Estimates from the GBD 2019 study, coordinated by the Institute for Health Metrics and Evaluation, were used for the analysis of trends in prevalence, DALYs and deaths of metabolic diseases and risk factors such as T2DM, HTN, HLD, obesity and NAFLD from the year 2000 to 2019. GBD 2019 is a multinational collaborative study across 204 countries and territories that is updated annually and designed to allow for consistent comparisons [9]. All data inputs can be obtained to generate estimates on the Global Health Data Exchange website [12]. We retrieved publication estimates of prevalence, deaths, DALYs, and YLDs for each metabolic disease, namely T2DM and NAFLD; and estimates of deaths, DALYs, and YLDs for HLD, HTN, and obesity, which were classified as metabolic risk factors rather than diseases in the GBD. Furthermore, as current clinical practice guidelines [13] recommend the evaluation of atherosclerotic cardiovascular disease risk in individuals aged 40 years and above, this study intends to examine the metabolic burden in younger adults who might be left undetected based on present risk stratification strategies [14]. As such, the GBD estimates were stratified to ages 15–39 years to obtain data on the metabolic diseases and risk factors in the younger adult population. Annual percentage change (APC) in rates was compared using a Joinpoint Regression Model to observe the trends in the metabolic diseases and risk factors over time when stratified by sex, location, and SDI. Aggregate prevalence, deaths, DALYs, and YLDs for each disease entity were obtained via International Classification of Diseases-10 (ICD-10) codes. Given the potential overlap of conditions in the same individual, we did not provide combined estimates of different metabolic diseases. The full details on the methods used to generate the GBD estimates have been described previously [15, 16] (Supplementary Material 1).

In terms of disease projections, historical data between 2000 and 2019 were tested for linear and quadratic trends. Based on visual inspection and evaluation of the models, we chose the most appropriate model with the best fit for each disease entity and population group. Using the predictions from the regression models and the Institute for Health Metrics and Evaluation projection [17] of population counts for years 2022–2050, we projected the burden of mortality and DALYs through to year 2050 for each metabolic disease entity. To examine the percentage change for each metabolic disease, the following equation was used:

$$Estimated\ percentage\ change$$

$$= \frac{(Estimates\ at\ the\ end\ of\ 5\ year\ period) - (Estimates\ at\ the\ start\ of\ 5\ year\ period)}{Estimates\ at\ the\ start\ of\ 5\ year\ period} \times 100\%.$$

The full details on the methods used to project GBD estimates have been described previously [18].

2.2 Death, DALYs, and YLDs Estimation in GBD 2019 Study

The primary outcome was mortality while secondary outcomes included prevalence, DALYs and YLDs. These estimates were retrieved through standardisation of input data and mapping of ICD-10 using methods of estimation employed by previous GBD studies [10, 11]. Age-standardised prevalence, death, DALY and YLD estimates were described with 95% uncertainty intervals (UIs), and the APC was presented with 95% confidence interval (CIs) of the age-standardised rates for the study period. An APC of 1% indicates a 1% increase per year while an APC of -0.5% indicates a 0.5% decrease per year.

2.3 Disease Prevalence, Socio-Demographic Index and World Health Organisation Regions

SDI was used as a composite measure of the average rankings of incomes per capita, average educational attainment and fertility rates [19] of the countries and territories [11]. This index is expressed on a scale of 0-1. An SDI of 0 indicates a theoretical minimum level of development relevant to health, while an SDI of 1 is the theoretical maximum and was used to classify the countries into high, high-middle, middle, low-middle, and low SDI countries. Data was stratified based on the WHO regions [20], namely Africa, Eastern Mediterranean, Europe, Region of Americas, South-East Asia, and Western Pacific. All statistical analysis was performed using Joinpoint Regression version 4.9.1.0 and STATA version 17.0.

3. RESULTS

3.1 Overview

In 2019, there was an estimated prevalence of 53.8 million and 425.8 million cases of T2DM and NAFLD respectively in young adults. The highest mortality was related to HTN with 219,545 deaths, followed by obesity with 182,167 deaths, HLD with 144,374 deaths, T2DM with 23,355 deaths, and NAFLD with 10,971 deaths. From 2000 to 2019, there were annual declines in age-standardised mortality rates for T2DM (-0.20%), HLD (-0.60%) , HTN (-0.47%) and NAFLD (-0.31%). In contrast, there was an annual increase of 1.07% in death rates for obesity (Figure 1A). Annual declines in age-standardised DALYs were observed for NAFLD (-0.33%), HTN (-0.32%), HLD (-0.55%); whereas there were annual increases for obesity (1.48%) and T2DM (1.35%) between 2000-2019 (Figure 1B). Similarly, there were annual increases in YLDs related to obesity and T2DM, but not in NAFLD, HTN, and HLD (Supplementary Figure 1). The largest proportion of mortality was observed in HTN (Figure 2A), whilst majority of metabolic-related DALYs and YLDs were related to obesity (Figure 2B, Supplementary Figure 2).

3.2 Type 2 Diabetes Mellitus

3.2.1 Global Prevalence

The age-standardised prevalence rate of young adults with T2DM in 2019 was 5,283 (95% UI 4,854 to 5,752) per 100,000 population. There was a 2.07% annual increase in T2DM-related prevalence from 2000 to 2019 (2.29% increase in males and 1.81% in females). Larger annual increase of T2DM prevalence was observed in countries with increasing SDI, from 1.32% in low SDI to 3.08% in high SDI countries (Supplementary Table 1).

3.2.2 Diabetes-Related Mortality

The age-standardised death rate in individuals with T2DM in 2019 was 18.49 (95% UI 17.18 to 19.66) per 100,000 population. T2DM-related mortality rates decreased (-0.20%) from 2000 to 2019. Significant annual reduction was observed in females (-0.44%) but not in males (Table 1).

3.2.3 Diabetes-Related Mortality Differences Based on Geographical Region and SDI

The change in T2DM-related mortality from 2000 to 2019 varied across geographical regions, with the largest reduction in South-East Asia (-1.03%), while the Eastern Mediterranean (1.59%) observed increased mortality rates (Supplementary Figure 3). In 2019, T2DM-related death rates were the highest in Africa (39.30 [95% UI 35.50 to 43.36]) and Eastern Mediterranean (32.26 [95% UI 28.22 to 36.22]); whilst Western Pacific (10.42 [95% UI 9.28 to 11.45]) and Europe (10.22 [95% UI 9.32 to 10.89]) had the lowest.

An estimated 22,260 deaths (95.3% of total deaths) related to T2DM occurred in low to high-middle SDI countries. T2DM-related death rate in 2019 was the lowest in high SDI (9.05 [95% UI 8.29 to 9.55]] and highest in low SDI countries (31.89 [95% UI 28.95 to 35.05]). From 2000 to 2019, reduction of T2DM-related death rates was only reported in high SDI (-0.83%) and high-middle SDI countries (-0.58%).

3.2.4 Diabetes-Related DALYs and YLDs

In 2019, there was an estimated 4.5 million T2DM-related DALYs, with an APC of 1.35% from 2000 to 2019. Males experienced a larger annual increase in DALYs (1.58%) than females (1.04%). There were 3.2 million YLDs related to T2DM, with an annual increase of 2.11% from 2000 to 2019.

3.3 Hypertension

3.3.1 Hypertension-Related Mortality

In 2019, the age-standardised death rate in individuals with HTN was 138.88 (95% UI 121.25 to 155.73) per 100,000 population. There was a decrease in HTN-related mortality rate from 2000 to 2019, with annual reduction of -0.47%; although significant reduction was observed only in females (-1.37%) (Table 2).

3.3.2 Hypertension-Related Mortality Differences Based on Geographical Region and SDI

In 2019, Eastern Mediterranean had the highest age-standardised death rates of 242.78 (95% UI 207.76 – 277.97) per 100,000 population. From 2000 to 2019, the largest decrease in HTN-related mortality rates was seen in South-East Asia (-1.14%), whilst the Eastern Mediterranean observed an annual increase of 0.81% (Supplementary Figure 4).

In 2019, an estimated 209,080 deaths (95.2% of total deaths) occurred in low to high-middle SDI countries. The age-standardised death rates of HTN were lowest at 69.76 (95% UI 58.67 to 79.66) in high SDI, and highest in low SDI countries at 169.85 (95% UI 147.99 to 191.20). There were decreases in HTN-related death rates from 2000 to 2019 in all countries, with the largest recorded in high-middle SDI countries.

3.3.3 HTN-Related DALYs and YLDs

In 2019, there were 13.9 million HTN-related DALYs, with an annual reduction of -0.32% from 2000 to 2019. This reduction in DALYs was only observed in females. YLDs related to HTN was estimated to be 1.7 million, with an annual increase of 1.06% over time.

3.4 Non-alcoholic Fatty Liver Disease

3.4.1 Prevalence of NAFLD

In 2019, the age-standardised prevalence rate of NAFLD was 15,023 (95% UI 13,494 to 16,765) per 100,000 population. The annual increase in NAFLD-related prevalence rates was 1.01%, with a larger increase in males (1.18%) than in females (0.81%). The age-standardised prevalence rates were highest in the Eastern Mediterranean region (24,762 [95% UI 22,600 to 27,110]) and lowest in Europe (12,502 [95% UI 11,260 to 13,832]). The Western Pacific (1.40%) observed the largest increase in prevalence rates from 2000 to 2019 (Supplementary Table 2).

3.4.2 NAFLD-Related Mortality

In 2019, the age-standardised death rate in individuals with NAFLD was 2.09 (95% UI 1.61 to 2.60) per 100,000 population. Between 2000–2019, the annual reduction in NAFLD-related death rate was -0.31%. This decrease was only significant in females (-0.73%) (Table 3).

3.4.3 NAFLD-Related Mortality Differences Based on Geographical Region and SDI

In 2019, NAFLD-related age-standardised death rates were the highest in Eastern Mediterranean (4.13 [95% UI 2.91 to 5.68]). There were increases in death rates for NAFLD from 2000 to 2019 in

Europe (2.39%) and Eastern Mediterranean (0.48%), but reductions in Western Pacific (-2.28%), South-East Asia (-0.85%), and Africa (-0.32%) (Supplementary Figure 5).

In 2019, 10,484 deaths (95.6% of total death) related to NAFLD occurred in low to high-middle SDI countries. The NAFLD-related age-standardised death rates generally decreased in countries with increasing SDI, with the lowest in high SDI (1.37 [95% UI 1.07 to 1.72]) and highest in low SDI countries (2.79 [95% UI 2.05 to 3.74]). From 2000 to 2019, the largest decrease in death rates was seen in the high SDI countries (-0.92%).

3.4.4 NAFLD-Related DALYs and YLDs

In 2019, 630,891 DALYs were estimated to be related to NAFLD, with annual reduction of -0.33% in DALYs from 2000 to 2019. This reduction was only significant in females (-0.74%). There were 7,435 YLDs related to NAFLD, with an annual increase of 0.38% over time.

3.5 Hyperlipidaemia

3.5.1 HLD-Related Mortality

In 2019, the HLD-related age-standardised death rate was 56.51 (95% UI 41.83 to 73.62) per 100,000 population. There was an annual reduction in HLD-related death rates of -0.60% from 2000 to 2019, which was more pronounced in females (-1.37%) than in males (-0.26%) (Table 4).

3.5.2 Hyperlipidemia-Related Mortality Differences Based on Geographical Region and SDI

Age-standardised death rate of HLD was highest in Eastern Mediterranean (110.64, 95% UI 82.10 to 142.21), and lowest in Region of Americas (40.44, 95% UI 30.00 to 52.53). From 2000 to 2019, the largest decrease in death rates was observed in Europe (-1.91%) (Supplementary Figure 6).

In 2019, 136,716 deaths (94.7% of all deaths) related to HLD occurred in low to high-middle SDI countries. The age-standardised death rate was lowest in high SDI countries (32.94 [95% UI 24.03 to 43.46]) and highest in high-middle SDI (70.67 [95% UI 51.79 to 93.69]). The largest decrease in the death rates from 2000 to 2019 was observed in high-middle (-1.37%) SDI countries.

3.5.3 Hyperlipidemia-Related DALYs and YLDs

In 2019, 8.5 million DALYs were estimated to be related to HLD, with an annual change of -0.55%. A larger reduction of DALYs was observed in females (-1.23%) than in males (-0.23%). Conversely, there were 603,592 YLDs related to HLD, with an annual increase (0.33%) from 2000 to 2019.

3.6 Obesity

3.6.1 Obesity-Related Mortality

The 2019 age-standardised death rate related to obesity was 62.59 (95% UI 39.92 to 89.13) per 100,000 population. From 2000 to 2019, death rates increased by 1.07% annually, with a larger increase in males (1.61%) than in females (0.22%). There was an estimated 15.2 million DALYs related to obesity in 2019, with 1.48% annual increase in DALY rates from 2000 to 2019 (Table 5).

3.6.2 Obesity-Related Mortality Differences Based on Geographical Region and SDI

The highest obesity-related age-standardised death rate in 2019 was seen in the Eastern Mediterranean region (130.97, 95% UI 87.38 to 179.78), and the lowest in Western Pacific (38.38, 95% UI 18.10 to 64.89). From 2000 to 2019, South-East Asia (1.76%) and Western Pacific (1.72%) regions reported the largest increases in obesity-related death rates; with only Europe (-0.56%) observing a decrease (Figure 3).

In 2019, 168,969 obesity-related deaths (92.8% of total deaths) occurred in low to high-middle SDI countries. The death rate was the lowest in the high SDI (46.65 [95% UI 29.76 to 63.76]), and the highest in the high-middle SDI countries (69.14 [95% UI 44.00 to 98.24]). Increase in obesity-related death rates from 2000 to 2019 was highest in low-middle SDI countries (2.11%), with no changes in death rates observed in high and high-middle SDI countries.

3.6.3 Obesity-Related DALYs and YLDs

In 2019, an estimated 15.2 million DALYs were related to obesity, with annual increase of 1.48% from 2000 to 2019. Males had larger increases in DALYs (1.91%) than females (0.95%). There were 5.0 million YLDs related to obesity, with annual increase of 2.50% from 2000 to 2019.

3.7 Projected Deaths and DALYs

By the year 2050, the largest burden of deaths is projected to be related to obesity with 369,492 deaths (102.8% increase from 2019), followed by HTN with 354,256 deaths (61.4% increase), HLD with 232,224 deaths (60.8% increase), T2DM with 60,405 deaths (158.6% increase), and NAFLD with 28,345 deaths (158.4% increase) (Figure 4; Supplementary Table 3). From 2019 to 2050, males will continue to bear the larger burden of deaths compared to females for all metabolic diseases (Supplementary Figure 7). However, females are projected to have a larger percentage increase in HTN and HLD-related deaths and DALYs (Supplementary Table 4).

The largest burden of DALYs, by the year 2050, will be found in obesity with 31.6 million DALYs (108.0% increase from 2019), followed by HTN with 22.3 million DALYs (61.6% increase), HLD with 13.9 million DALYs (64.3% increase), T2DM with 10.1 million DALYs (123.4% increase), and NAFLD with 1.6 million DALYs (153.8% increase) (Supplementary Table 5). The fastest increase in HTN, HLD, NAFLD, and obesity-related DALYs is projected to occur between years 2035 and 2040 (Figure 5). From 2019 to 2050, males will continue to have higher DALYs compared to females for all metabolic diseases.

4. DISCUSSION

Previous GBD studies depicted the young population's metabolic burden by examining each disease entity in silos. The main driver of incident chronic liver diseases amongst the young adult population has shifted from viral hepatitis to NAFLD [8], mirroring the rising obesity prevalence as elucidated by earlier GBD 2013 studies [21]. Moreover, the socioeconomic and geographical disparity in the incidence of metabolic diseases, such as diabetes [7], is already evident as early as young adulthood. However, as metabolic diseases share similar upstream pathomechanistic processes and underlying societal drivers, the present consortium adds to the present literature by consolidating the metabolic diseases under the umbrella concept of the 'Global Metabolic Syndemic' affecting the young adult population. This provides a valuable construct in comparing the trends of the metabolic components, as well as projecting the burden of metabolic diseases in the decades ahead (Graphical Abstract). The data portray the concerning findings of the growing burden of metabolic diseases and risk factors such as T2DM, HTN, HLD, obesity and NAFLD, which parallels the global shift in lifestyle practices that has already made its impact on our young adults. The rising disease burden over the past two decades, with obesity and HTN identified as the main drivers of the global burden of metabolic disease, allows stakeholders to implement effective strategies in targeting the entrenched contributors. The WHO estimates that 70% of worldwide premature deaths stem from behaviours begun in adolescence and young adulthood [22]. The study predicts that obesity will surpass HTN as the main contributor of metabolic disease-related deaths and DALYs in the years ahead. This offers a critical opportunity to inform important stakeholders in prioritising upstream solutions to tackle the silent obesity epidemic and curb the incidence of metabolic diseases globally, through effective interventions that address underlying social and economic precursors of metabolic risks in young adults. Unhealthy behaviours that perpetuate later into life often become challenging to modify, as reflected by the lack of success in sustained metabolic improvement with lifestyle interventions [23-26].

The putative biological underpinnings of the metabolic wave, dominated by the rising obesity epidemic, are complex and often share close and bidirectional associations with other metabolic disorders. Visceral obesity increases lipotoxicity, insulin resistance, pro-inflammatory mediators (such as interleukin-6, C-reactive protein) that can accelerate the metabolic sequalae [27, 28]. Although

metabolic diseases are often interdependent, recent evidence has suggested that each metabolic disorder may have independent associations with adverse cardiovascular prognosis. For instance, NAFLD increases the risk of chronic kidney disease, stroke [29, 30] and cardiovascular diseases [31], independent of T2DM and HTN. Nevertheless, the focus on metabolic health in the young adult population is critical in halting the downstream effects of disparate metabolic health that may persist across generations. Population-based studies have demonstrated that low and high birth weights are associated with deleterious long-term metabolic health, including obesity, fasting glucose impairment, HTN, NAFLD, hypertriglyceridemia, and HLD [32]. Societal drivers such as poorer education levels, especially in socioeconomically disadvantaged populations, were also reported to perpetuate the disparate birth weight within the population [32, 33].

Even though the disparity in mortality rates across sex, geographical and socioeconomic factors have been described in previous GBD studies [9], we highlight that this disparity begins as early as young adulthood across metabolic diseases. The most significant decreases in mortality for T2DM, HTN, HLD and NAFLD were observed in females, with the largest increase in obesity-related mortality seen in males. This sex disparity in favour of women is likely multifactorial, with biological advantages related to the protective effect of oestrogen on the risk of metabolic disease [34], as well as fat distribution and pattern of fat loss between both sexes [35]. This highlights the importance of developing targeted and sex-specific strategies when addressing metabolic diseases in the young population [24]. Moreover, the considerable variation in mortality across geographical regions, particularly with excess mortality predominantly in the Middle Eastern and African regions, may be contributed by the deeply entrenched social and cultural factors [36], as well as biological differences in fat patterning, body composition and cardiometabolic effects of a high body mass index [37]. In addition, there is a sense of urgency in tackling the disparate burden of metabolic diseases in the young population, given the paradoxical trends of the lower prevalence but higher mortality burden of disease in low SDI countries. This disparity is further exacerbated by the gradient of increasing prevalence yet lower mortality burden across the countries with increasing SDI quintile.

Despite the global efforts to tackle the rising epidemic of metabolic diseases [38], the unabated rise in the global prevalence of metabolic diseases over the past two decades is of concern. This consortium

projects the global burden of metabolic diseases that will be expected to continue to rise with worrisome trends. The projected increase in deaths and DALYs will disproportionately affect males more than females, but females are predicted to see a larger increase in the burden of HTN and HLD in the future. A particularly striking result is the dominance of obesity, surpassing HTN, as the main contributing disease for both deaths and DALYs in the future [39, 40]. Indeed young adults have been increasingly exposed to the obesogenic environment attributed to increased globalisation, interconnectivity, technological advancements, decreases in activity and the convenience of energy-rich foods [41]. The significant increases in obesity-related mortality and DALYs over the years draw concerns over the potential delayed disease progression of obesity to other metabolic manifestations [42, 43]. With increasing life expectancy, the global burden of metabolic diseases is bound to rise further if these shared metabolic drivers are not addressed effectively [44]. The projections from this study may serve as a motivator and help modify policy development in implementing preventive strategies with a more targeted sex-specific approach with emphasis on risk stratification and interventions focused on tackling the root causes of obesity and metabolic disease differences in the ever-changing populations [18]. Concerted efforts in addressing sex- and cultural-specific barriers and facilitators to weight management and health literacy are crucial in addressing the global disparity [45]. Similarly, pharmacological agents should target the reduction of the overall metabolic milieu rather than a disease in isolation [46]. Emerging evidence on the beneficial effects of glucagon-like peptide-1 receptor agonists (GLP1-RA) that help improve weight loss, reduce hepatic fat, glycemic levels and importantly, cardiovascular events [47], offer hope for future reduction in obesity-related mortality [48].

4.1 Strengths and Limitations

This study takes advantage of the ‘Global Metabolic Syndemic’ framework and compares the trends of all metabolic diseases in the young adult population, stratified based on sex, geographical regions and socioeconomic standing. The findings are essential in informing policymaking strategies with the projection of the global metabolic burden up to 2050. Moreover, the GBD 2019 study is one of the most comprehensive worldwide databases of diseases and has been utilised by various policy-makers globally to direct public health policy. The GBD has made several comprehensive efforts to ensure accurate GBD estimates, accountability, comparability of measurement, and generalisability

[49]. In our study, we have included the complete data estimates derived from the GBD 2019 study, thus allowing the findings to represent the broader populations [49]. However, this study is not without its limitations. First, the GBD data's reliability depends on the quality and availability of the individual country's vital registration system. However, in areas without data sources, GBD estimates rely on the modelling processes, predictive covariates and temporal trends derived from neighbouring countries that may lead to inherent biases [16]. Nevertheless, GBD has managed this issue over the years by reinforcing annual searches with in-country collaborators for available data, enforcing data cleaning, correction, and maximising data utility. Second, even though metabolic diseases often occur as a cluster of diseases and metabolic risk factors that collectively increases the risk of atherosclerotic cardiovascular diseases [4, 50-52], the lack of granularity in individual patient data within the database did not allow the examination of the synergistic or additive effects of the combination of metabolic diseases. As such, this study could only compare the trends of each metabolic component.

4.2 Future Directions

With the unified goal to reduce the burden of metabolic disease in future decades, the present study emphasises the importance of addressing the shared drivers of metabolic diseases from a young age [53]. To further future research that can have a significant impact on clinical decision-making, we propose the 'Global Metabolic Syndemic' framework, or the synergy of epidemics as described by the *Lancet* Obesity Commission [54], since these metabolic diseases often exist in tandem, share common pathomechanistic pathways and underlying societal drivers, that collectively contribute to the development of cardiovascular disease [55-59], disability, cancers, and premature deaths [7, 16]. Historically, each metabolic entity was considered in isolation, but consolidating the collective metabolic burden into a single global syndemic framework can help focus the attention on addressing the combined challenges and reminds us of the importance of prioritising standard upstream solutions in order to mitigate the overall metabolic milieu of the individual [4, 54]. Stakeholders can shift their attention to developing sex-, geographical- and socioeconomic-specific programs to enhance the screening, detection and prevention of metabolic diseases in young adults that have the potential benefit of reducing healthcare demands and spending.

The integration of population health and biomedical sciences through the strategic partnerships between researchers, clinicians and policymakers can facilitate the implementation of novel translational discoveries into clinical practice. With the pursuit of the first US Food and Drug Administration-approved NAFLD therapeutics in the pipeline, now being evaluated in late-stage clinical trials, future translational studies are warranted to explore the additional metabolic effects of these therapeutics (namely peroxisome proliferator-activated receptor agonists, GLP1-RA) on the overall metabolic milieu such as insulin sensitivity, de-novo lipogenesis, and weight reduction [25, 60]. The enthusiasm for discovering novel therapeutics and their benefits on metabolic health is ever-increasing but should maintain the importance of lifestyle modifications and optimisation of cardiovascular comorbidities.

5. Conclusion

The growing burden of metabolic diseases over the past two decades, accompanied by the increasing obesity-related mortality trends, presents a significant global burden of metabolic diseases now and in the years ahead. The disparities in the burden of metabolic diseases stem from entrenched sex-regional-socioeconomic precursors that begin as early as young adulthood. The focus on young people is paramount, and there is a sense of urgency in implementing effective preventative and therapeutic strategies at the individual, communal and national levels to derail the projected trajectory of the metabolic burden.

FIGURE LEGENDS

Graphical abstract. The 'Global Metabolic Syndemic' framework.

Figure 1. A) Number of deaths and age-standardised death rates and B) disability-adjusted life year (DALYs) and Age-standardised DALYs in individuals less than 40 years of age, at the global level by the five metabolic diseases, 2000-2019

Bar charts depict the total Deaths/DALYs and line graphs depict the age-standardised rates of Deaths/DALYs

Figure 2. A) Proportion of deaths and, B) Proportion of disability-adjusted life years (DALYs) due to the five metabolic diseases in individuals less than 40 years of age, at global and regional levels by sex, 2019

Figure 3. The global trends of a) age-standardised mortality and b) percentage change in obesity in individuals less than 40 years of age

Figure 4. Projection of Disease-adjusted Life Years (DALYs) by disease from 2020 to 2050

Figure 5. Bar graph of Percentage Change of Disability-adjusted Life Years (DALYs) by disease from 2020 to 2050

DATA SHARING

Data used in the analyses is publicly available, and can be found on the Global Health Data Exchange GBD 2019 website.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Bryan Chong: Methodology, Investigation, Data curation, Formal analysis, Writing - original draft, review & editing

Gwyneth Kong: Methodology, Investigation, Data curation

Kannan Shankar: Methodology, Investigation, Data curation, Formal analysis, Writing - original draft, review & editing

HS Jocelyn Chew: Data curation, Writing - review & editing

Chaoxing Lin: Investigation, Data curation, Formal analysis

Rachel Goh: Investigation, Data curation, Formal analysis

Yip Han Chin: Investigation, Data curation, Formal analysis

Darren Jun Hao Tan: Validation, Writing - review & editing

Kai En Chan: Validation, Writing - review & editing

Wen Hui Lim: Validation, Writing - review & editing

Nicholas Syn: Data curation, Writing - review & editing

Siew Pang Chan: Investigation, Data curation, Formal analysis

Jiong-Wei Wang: Supervision, Writing - review & editing

Chin Meng Khoo: Supervision, Writing - review & editing

Georgios Dimitriadis: Supervision, Writing - review & editing

Karn Wijarnpreecha: Supervision, Writing - review & editing

Arun Sanyal: Supervision, Writing - review & editing

Mazen Noureddin: Supervision, Validation Writing - review & editing

Mohammad Shadab Siddiqui: Supervision, Writing - review & editing

Roger Foo: Supervision, Writing - review & editing

Anurag Mehta Supervision, Writing - review & editing

Gemma Figtree: Supervision, Writing - review & editing

Derek Hausenloy: Supervision, Writing - review & editing

Mark Chan: Supervision, Validation, Writing - review & editing

Cheng Han Ng: Conceptualization, Supervision, Writing - review & editing

Mark Muthiah: Supervision, Writing - review & editing

Mamas A Mamas: Methodology, Data curation, Supervision, Validation, Writing - review & editing

Nicholas WS Chew: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Software, Supervision, Validation, Writing - original draft, review & editing

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Table 1. Disability-adjusted life years and mortality of individuals less than 40 years of age with type 2 diabetes mellitus

	DALYs			Mortality		
	Number, 2019	Age-standardised DALYs per 100000, 2019	Annual percentage change, 2000-2019 (%)	Number, 2019	Age-standardised death rate per 100000, 2019	Annual percentage change, 2000-2019 (%)
Overall	4,522,183 (3,336,755 – 5,989,091)	801.55 (670.58 - 954.43)	1.35 (1.25 to 1.44)	23,355 (21,114 – 26,586)	18.49 (17.18 - 19.66)	-0.20 (-0.30 to -0.09)
Sex						
Male	2,441,722 (1,792,150 – 3,243,279)	865.16 (721.20 - 1030.70)	1.58 (1.44 to 1.72)	12,631 (11,254 – 14,236)	19.94 (18.50 - 21.32)	0.18 (-0.05 to 0.41)
Female	2,080,461 (1,531,567 - 2,770,615)	743.71 (621.81 - 888.99)	1.04 (0.86 to 1.21)	10,724 (9,312 – 12,763)	17.30 (15.62 - 18.70)	-0.44 (-0.65 to -0.24)
WHO region						
Africa	520,752 (402,305 – 664,665)	1142.91 (992.15 - 1311.64)	0.11 (0.01 to 0.20)	4,051 (3,238 – 5,186)	39.30 (35.50 - 43.36)	-0.96 (-1.12 to -0.80)
Eastern Mediterranean	552,628 (405,693 – 731,637)	1229.76 (1029.01 - 1455.02)	2.19 (2.08 to 2.29)	3,123 (2,486 – 3,839)	32.26 (28.22 - 36.22)	1.59 (1.42 to 1.76)
Europe	333,823 (221,026 – 475,580)	565.64 (441.23 - 703.95)	1.89 (1.80 to 1.97)	670 (570 - 828)	10.22 (9.32 - 10.89)	-0.59 (-0.84 to -0.34)
Region of Americas	655,968 (501,311 – 847,661)	1023.75 (854.17 - 1228.65)	1.59 (1.41 to 1.77)	3,967 (3,547 – 4,610)	22.55 (20.65 - 24.08)	0.28 (-0.08 to 0.64)
South-East Asia	1,477,626 (1,098,579 – 1,939,964)	1081.58 (917.95 - 1269.13)	0.67 (0.56 to 0.79)	7,931 (6,740 – 9,296)	29.41 (26.42 - 32.31)	-1.03 (-1.41 to -0.65)
Western Pacific	967,510 (677,386 – 1,352,396)	526.68 (426.24 - 643.71)	1.79 (1.50 to 2.08)	3,544 (3,181 – 3,971)	10.42 (9.28 - 11.45)	-0.59 (-1.12 to -0.07)
SDI						

High	401,317 (272,381 – 561,681)	584.69 (454.63 - 735.02)	2.29 (2.21 to 2.37)	1,057 (939 – 1,293)	9.05 (8.29 - 9.55)	-0.83 (-1.15 to -0.50)
High-middle	684,055 (470,068 – 958,430)	610.16 (492.12 - 743.69)	1.84 (1.67 to 2.01)	2,151 (1,961 – 2,390)	12.65 (11.58 - 13.53)	-0.58 (-0.76 to -0.39)
Middle	1,585,942 (1,197,225 – 2,067,569)	915.14 (780.40 - 1075.78)	1.24 (1.04 to 1.46)	9,179 (8,372 – 10,097)	23.74 (21.97 - 25.52)	-0.06 (-0.32 to 0.19)
Low-middle	1,223,162 (912,684 – 1,591,899)	1049.75 (891.23 - 1231.42)	1.10 (0.99 to 1.21)	6,853 (5,925 – 8,185)	29.05 (26.46 - 31.48)	-0.23 (-0.54 to 0.08)
Low	622,775 (471,094 – 813,742)	1064.45 (915.04 - 1236.74)	0.45 (0.40 to 0.51)	4,077 (3,360 – 5,100)	31.89 (28.95 - 35.05)	-0.67 (-0.78 to -0.56)

Data in the parentheses are 95% uncertainty intervals· DALYs, disability-adjusted life year; SDI, Socio-Demographic Index; WHO, World Health Organisation

Table 2. Disability-adjusted life years and mortality of individuals less than 40 years of age with hypertension

	DALYs			Mortality		
	Number, 2019	Age-standardised DALYs per 100000, 2019	Annual percentage change, 2000-2019 (%)	Number, 2019	Age-standardised death rate per 100000, 2019	Annual percentage change, 2000-2019 (%)
Overall	13,852,353 (11,462,774 – 16,334,355)	2885.57 (3201.05 - 2580.75)	-0.32 (-0.50 to -0.14)	219,545 (179,619 – 259,259)	138.88 (155.73 - 121.25)	-0.47 (-0.67 to -0.27)
Sex						
Male	9,452,095 (7,741,417 – 11,086,945)	3448.86 (3837.69 - 3060.06)	0.06 (-0.13 to 0.25)	155,408 (126,544 – 183,701)	160.13 (180.79 - 138.91)	-0.04 (-0.25 to 0.17)
Female	4,400,258 (3,589,141 – 5,343,791)	2354.72 (2634.68 - 2075.57)	-1.00 (-1.19 to -0.82)	64,138 (51,721 – 78,550)	119.66 (136.86 - 102.33)	-1.37 (-1.58 to -1.16)
WHO region						
Africa	1,824,138 (1,478,014 – 2,204,384)	3659.56 (4131.92 - 3181.90)	-0.71 (-0.87 to -0.55)	27,741 (22,255 – 33,688)	181.33 (205.66 - 156.44)	-0.95 (-1.12 to -0.78)
Eastern Mediterranean	2,157,375 (1,692,668 – 2,692,270)	5074.19 (5798.52 - 4376.45)	0.90 (0.82 to 0.98)	34,875 (26,705 – 44,201)	242.78 (277.97 - 207.76)	0.81 (0.76 to 0.87)
Europe	1,330,535 (1,119,056 – 1,540,178)	2665.22 (2955.47 - 2359.53)	-0.64 (-1.19 to -0.08)	21,334 (17,770 – 24,826)	136.32 (153.92 - 115.61)	-0.84 (-1.46 to -0.22)
Region of Americas	1,166,554 (972,934 – 1,373,149)	1963.08 (2181.60 - 1731.93)	0.26 (0.08 to 0.44)	17,409 (14,383 – 20,520)	93.91 (105.76 - 80.49)	0.04 (-0.15 to 0.23)
South-East Asia	4,530,363 (3,649,706 – 5,569,998)	3433.30 (3885.95 - 2995.78)	-1.05 (-1.40 to -0.71)	74,040 (59,118 – 91,310)	156.60 (178.92 - 134.95)	-1.14 (-1.53 to -0.74)
Western Pacific	2,819,312 (2,122,202 – 3,566,785)	2558.28 (2925.37 - 2201.62)	-0.13 (-0.63 to 0.37)	43,793 (32,488 – 55,612)	127.80 (148.73 - 107.91)	-0.35 (-0.89 to 0.19)
SDI						
High	707,377 (586,145 – 834,981)	1385.57 (1545.55 - 1222.65)	-0.34 (-0.47 to -0.22)	10,303 (8,461 – 12,277)	69.76 (79.66 - 58.67)	-0.61 (-0.74 to -0.48)

High-middle	2,341,397 (1,926,299 – 2,764,808)	2845.57 (3172.17 - 2528.64)	-0.60 (-0.80 to -0.41)	36,966 (30,316 – 43,854)	147.83 (168.89 - 126.74)	-0.85 (-1.08 to -0.63)
Middle	4,673,158 (3,813,567 – 5,540,466)	3383.27 (3767.07 - 3009.74)	-0.26 (-0.52 to 0.00)	73,389 (59,303 – 87,505)	168.54 (190.77 - 147.10)	-0.45 (-0.76 to -0.14)
Low-middle	4,051,861 (3,306,533 – 4,910,317)	3614.21 (4062.85 - 3195.63)	-0.37 (-0.68 to -0.06)	65,904 (53,174 – 79,902)	166.81 (189.46 - 144.97)	-0.47 (-0.81 to -0.12)
Low	2,068,411 (1,667,965 – 2,472,115)	3682.42 (4153.97 - 3212.75)	-0.39 (-0.61 to -0.18)	32,821 (26,365 – 39,597)	169.85 (191.20 - 147.99)	-0.54 (-0.75 to -0.34)

Data in the parentheses are 95% uncertainty intervals· DALYs, disability-adjusted life year; SDI, Socio-Demographic Index; WHO, World Health Organisation

Table 3. Disability-adjusted life years and mortality of individuals less than 40 years of age with non-alcoholic fatty liver disease

	DALYs			Mortality		
	Number, 2019	Age-standardised DALYs per 100000, 2019	Annual percentage change, 2000-2019 (%)	Number, 2019	Age-standardised death rate per 100000, 2019	Annual percentage change, 2000-2019 (%)
Overall	630,891 (400,694 – 951,720)	53.33 (40.73 - 68.29)	-0.33 (-0.47 to -0.19)	10,971 (6,934 – 16,632)	2.09 (1.61 - 2.60)	-0.31 to (-0.45 to -0.16)
Sex*						
Male	-	62.98 (47.70 - 81.89)	-0.05 (-0.24 to 0.13)	-	2.38 (1.82 - 3.02)	-0.03 (-0.22 to 0.15)
Female	-	43.92 (34.03 - 55.32)	-0.74 (-0.91 to -0.57)	-	1.82 (1.41 - 2.27)	-0.73 (-0.90 to -0.56)
WHO region						
Africa	98,458 (59,241 – 157,563)	84.58 (60.28 - 115.44)	-0.33 (-0.48 to -0.18)	1,681 (990 – 2,715)	3.59 (2.61 - 4.76)	-0.32 (0.47 to -0.18)
Eastern Mediterranean	52,070 (32,884 – 79,479)	83.17 (58.52 - 113.05)	0.43 (0.29 - 0.56)	883 (551 – 1,350)	4.13 (2.91 - 5.68)	0.48 (0.34 to 0.62)
Europe	88,224 (54,112 – 139,952)	51.95 (38.29 - 69.38)	2.32 (1.47 to 3.18)	1,573 (960 – 2,532)	1.82 (1.38 - 2.33)	2.39 (1.52 to 3.27)
Region of Americas	93,226 (57,001 – 138,268)	75.02 (56.27 - 97.08)	-0.06 (-0.30 to 0.19)	1,654 (1,003 – 2,488)	2.84 (2.16 - 3.60)	-0.03 (-0.28 to 0.21)
South-East Asia	222,544 (137,472 – 343,511)	58.22 (44.15 - 76.08)	-0.91 (-1.34 to -0.48)	3,838 (2,359 – 5,969)	2.35 (1.80 – 3.00)	-0.85 (-1.30 to -0.40)
Western Pacific	75,374 (51,581 – 106,735)	32.26 (25.28 - 39.96)	-2.25 (-2.54 to -1.97)	1,324 (892 – 1,901)	1.34 (1.07 - 1.63)	-2.28 (-2.57 to -2.00)
SDI						

High	27,082 (17,678 – 40,432)	34.16 (26.14 - 44.21)	-0.86 (-1.08 to -0.64)	480 (308 – 729)	1.37 (1.07 - 1.72)	-0.92 (-1.15 to -0.69)
High-middle	105,525 (66,991 – 163,258)	41.67 (31.71 - 53.60)	0.54 (-0.57 to 1.67)	1,877 (1,181 – 2,921)	1.57 (1.22 - 1.97)	0.48 (-0.59 to 1.57)
Middle	211,701 (139,203 – 316,269)	65.40 (50.66 - 82.14)	-0.74 (-1.05 to -0.43)	3,698 (2,403 – 5,559)	2.80 (2.17 - 3.52)	-0.72 (-1.03 to -0.41)
Low-middle	194,866 (120,979 – 295,574)	63.25 (47.35 - 82.85)	-0.24 (-0.52 to 0.03)	3,358 (2,071 – 5,121)	2.47 (1.88 - 3.16)	-0.20 (-0.48 to 0.08)
Low	91,294 (56,063 – 142,630)	68.06 (49.42 - 91.90)	-0.50 (-0.69 to -0.30)	1,551 (933 – 2,446)	2.79 (2.05 - 3.74)	-0.49 (-0.68 to -0.29)

Data in the parentheses are 95% uncertainty intervals· DALYs, disability-adjusted life year; SDI, Socio-Demographic Index; WHO, World Health Organisation

*The total counts for DALYs and mortality, stratified by sex, were not available for non-alcoholic fatty liver disease in the 2019 Global Burden of Diseases, Injuries and Risk Factors Study.

Table 4. Disability-adjusted life years and mortality of individuals less than 40 years of age with hyperlipidemia

	DALYs			Mortality		
	Number, 2019	Age-standardised DALYs per 100000, 2019	Annual percentage change, 2000-2019 (%)	Number, 2019	Age-standardised death rate per 100000, 2019	Annual percentage change, 2000-2019 (%)
Overall	8,516,576 (7,259,743 – 9,798,818)	1207.15 (1461.11 - 975.07)	-0.55 (-0.77 to -0.32)	144,374 (123,985 – 166,801)	56.51 (73.62 - 41.83)	-0.60 (-0.83 to -0.37)
Sex						
Male	5,936,732 (5,069,934 – 6,867,150)	1528.71 (1833.38 - 1250.26)	-0.23 (-0.43 to -0.03)	103,844 (88,816 – 120,544)	67.33 (86.43 - 50.78)	-0.26 (-0.47 to -0.05)
Female	2,579,845 (2,146,895 – 3,050,801)	898.27 (1120.41 - 706.02)	-1.23 (-1.49 to -0.96)	40,530 (33,729 – 48,214)	46.50 (62.38 - 32.70)	-1.37 (-1.67 to -1.07)
WHO region						
Africa	547,509 (418,218 – 686,304)	905.33 (1185.42 - 664.17)	-1.07 (-1.25 to -0.90)	8,827 (6,673 – 11,351)	44.39 (61.61 - 29.66)	-1.21 (-1.39 to -1.02)
Eastern Mediterranean	1,503,626 (1,229,542 - 1,828,134)	2463.93 (3015.32 - 1978.50)	0.00 (-0.06 to 0.07)	26,076 (21,134 – 31,921)	110.64 (142.21 - 82.10)	-0.05 (-0.12 to 0.02)
Europe	837,686 (730,078 – 968,460)	1417.78 (1717.22 - 1152.75)	-1.73 (-2.13 to -1.33)	14,153 (12,384 – 16,382)	70.89 (91.82 - 52.96)	-1.91 (-2.35 to -1.47)
Region of Americas	654,663 (572,590 – 735,494)	859.09 (1024.40 - 709.41)	-0.59 (-0.96 to -0.22)	10,816 (9,454 – 12,200)	40.44 (52.53 - 30.00)	-0.71 (-1.01 to -0.41)
South-East Asia	3,142,373 (2,556,148 – 3,743,832)	1350.06 (1672.30 - 1066.22)	-0.71 (-1.18 to -0.24)	54,824 (44,761 – 65,580)	56.40 (73.71 - 41.68)	-0.72 (-1.22 to -0.22)

Western Pacific	1,815,095 (1,515,178 – 2,101,638)	954.45 (1195.26 - 748.48)	0.04 (-0.52 to 0.61)	29,430 (24,511 – 34,072)	46.51 (63.24 - 32.62)	-0.02 (-0.64 to 0.61)
SDI						
High	482,226 (416,754 – 550,922)	673.60 (813.62 - 551.58)	-0.71 (-0.90 to -0.51)	7,561 (6,577 – 8,739)	32.94 (43.46 - 24.03)	-1.05 (-1.50 to -0.61)
High-middle	1,526,296 (1,334,282 – 1,716,682)	1372.12 (1671.72 - 1107.44)	-1.18 (-1.37 to -1.00)	25,411 (22,243 – 28,584)	70.67 (93.69 - 51.79)	-1.37 (-1.57 to 1.17)
Middle	3,087,122 (2,650,405 – 3,559,492)	1317.95 (1606.66 - 1060.41)	-0.14 (-0.43 to 0.16)	52,223 (44,808 – 60,340)	62.58 (82.53 - 45.48)	-0.15 (-0.47 to 0.18)
Low-middle	2,474,328 (2,065,900 – 2,940,613)	1367.46 (1676.50 - 1088.77)	-0.41 (-0.80 to -0.02)	43,015 (35,782 – 51,237)	58.35 (76.08 - 43.13)	-0.38 (-0.80 to 0.05)
Low	940,919 (762,423 – 1,150,381)	1166.15 (1456.01 - 908.99)	-0.57 (-0.78 to -0.35)	16,067 (12,907 – 19,777)	49.85 (66.37 - 35.97)	-0.62 (-0.85 to -0.40)

Data in the parentheses are 95% uncertainty intervals· DALYs, disability-adjusted life year; SDI, Socio-Demographic Index; WHO, World Health Organisation

Table 5. Disability-adjusted life years and mortality of individuals less than 40 years of age with obesity

	DALYs			Mortality		
	Number, 2019	Age-standardised DALYs per 100000, 2019	Annual percentage change, 2000-2019 (%)	Number, 2019	Age-standardised death rate per 100000, 2019	Annual percentage change, 2000-2019 (%)
Overall	15,193,290 (10,177,050 – 20,499,055)	1932.54 (2639.74 - 1276.61)	1.48 (1.30 to 1.65)	182,167 (123,264 – 245,353)	62.59 (89.13 - 39.92)	1.07 (0.97 to 1.16)
Sex						
Male	8,811,416 (5,670,539 – 12,112,115)	2070.34 (2888.83 - 1311.91)	1.91 (1.69 to 2.12)	116,602 (75,821 – 160,572)	66.55 (97.21 - 39.76)	1.61 (1.47 to 1.74)
Female	6,381,875 (4,488,005 – 8,600,223)	1789.67 (2417.12 - 1228.73)	0.95 (0.86 to 1.03)	65,566 (46,021 – 87,332)	58.14 (81.39 - 38.53)	0.22 (0.13 to 0.31)
WHO region						
Africa	1,623,162 (1,061,036 – 2,238,898)	2220.92 (3025.46 - 1485.78)	0.56 (0.43 to 0.70)	20,626 (13,074 – 28,980)	79.20 (111.98 - 50.92)	0.02 (-0.13 to 0.17)
Eastern Mediterranean	2,417,855 (1,696,683 – 3,241,718)	3721.05 (4953.94 - 2590.93)	1.31 (1.25 to 1.37)	31,246 (21,221 – 42,576)	130.97 (179.78 - 87.38)	0.90 (0.79 to 1.02)
Europe	1,679,307 (1,195,238 – 2,214,493)	2205.85 (2946.35 - 1518.77)	0.25 (-0.25 to 0.75)	17,073 (12,172 – 22,320)	75.41 (103.02 - 49.74)	-0.56 (-1.05 to -0.07)
Region of Americas	2,405,452 (1,780,116 – 3,126,585)	2456.96 (3199.65 - 1724.56)	0.86 (0.61 to 1.10)	22,852 (17,211 – 28,092)	72.83 (97.90 - 48.62)	0.17 (-0.21 to 0.55)
South-East Asia	4,193,342 (2,585,100 – 5,894,407)	1785.99 (2512.64 - 1096.44)	2.21 (1.97 to 2.45)	55,433 (33,856 – 79,326)	53.60 (78.85 - 31.54)	1.76 (1.44 to 2.08)

Western Pacific	2,834,177 (1,552,127 – 4,266,404)	1228.88 (1963.25 - 623.71)	2.25 (1.95 to 2.56)	34,532 (19,108 – 51,549)	38.38 (64.89 - 18.10)	1.72 (1.30 to 2.15)
SDI						
High	1,708,696 (1,219,812 – 2,267,641)	1631.11 (2198.13 - 1120.62)	1.03 (0.73 to 1.34)	13,033 (9,927 – 16,257)	45.65 (63.76 - 29.76)	0.12 (-0.18 to 0.41)
High-middle	2,751,679 (1851,763 – 3,715,897)	1981.83 (2705.52 - 1312.04)	0.88 (0.64 to 1.13)	31,493 (21,715 – 41,798)	69.14 (98.24 - 44.00)	0.16 (-0.06 to 0.39)
Middle	5,704,278 (3,943,841 – 7,504,875)	2118.58 (2920.07 - 1387.97)	1.74 (1.63 to 1.85)	71,367 (49,407 – 93,627)	68.92 (99.26 - 43.02)	1.29 (1.08 to 1.49)
Low-middle	3,536,659 (2,178,948 – 4,945,475)	1892.20 (2681.69 - 1174.34)	2.51 (2.33 to 2.70)	46,657 (28,492 – 66,007)	60.34 (88.37 - 36.27)	2.11 (1.85 to 2.36)
Low	1,478,757 (810,276 – 2,216,432)	1698.14 (2491.86 - 989.56)	1.71 (1.63 to 1.79)	19,452 (10,646 – 29,239)	55.55 (85.09 - 31.38)	1.33 (1.16 to 1.50)

Data in the parentheses are 95% uncertainty intervals· DALYs, disability-adjusted life year; SDI, Socio-Demographic Index; WHO, World Health Organisation

Figure 1

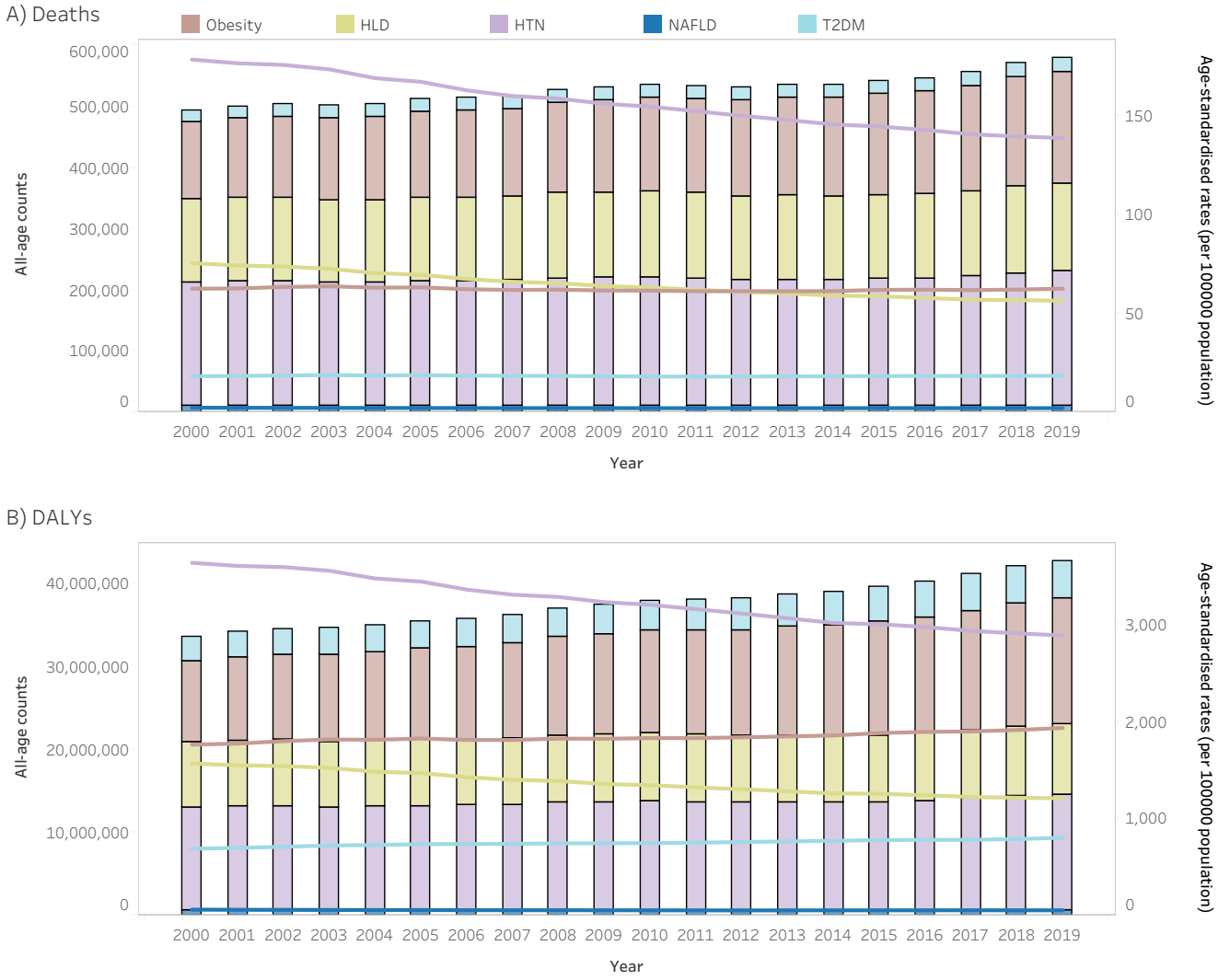
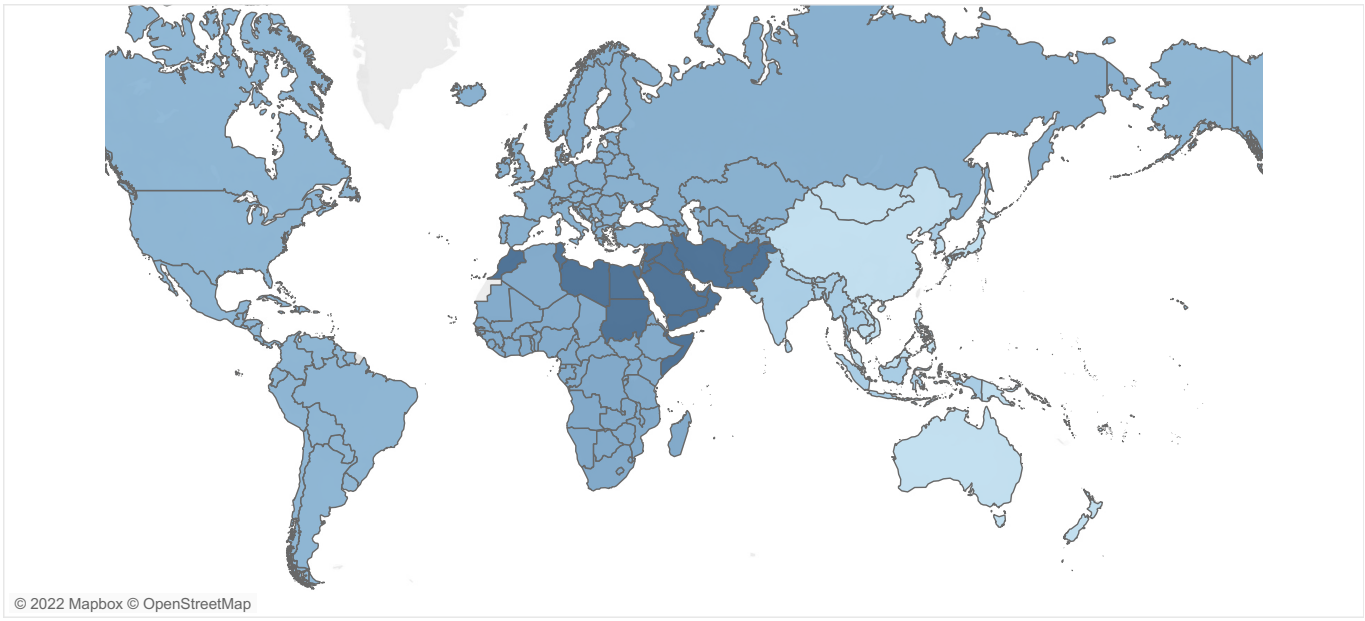


Figure 2

Click here to access/download;Figure;Figure 2.pdf

Figure 3

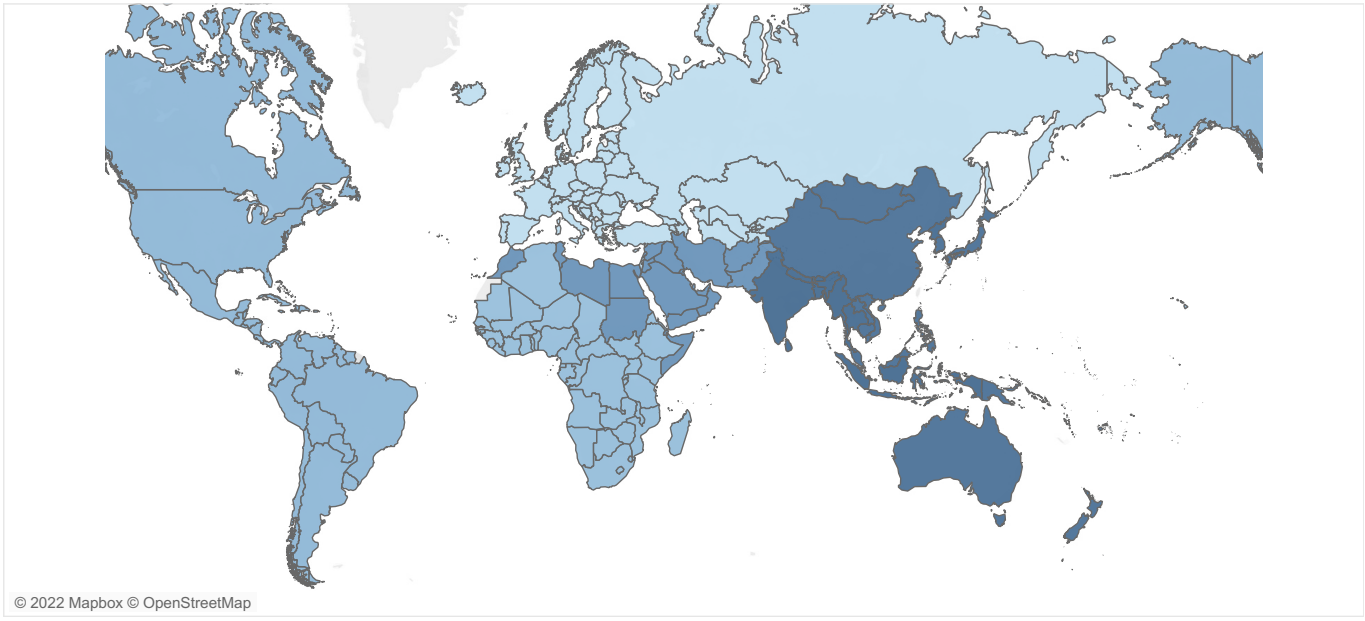
A) Obesity-related age-standardised death rate



Age-standardised death rate (per 100000 population)

- Western Pacific : 38.38 (18.10 - 64.89)
- Region of Americas : 72.83 (48.62 - 97.90)
- Africa : 79.20 (50.92 - 111.98)
- South-East Asia : 53.60 (31.54 - 78.85)
- Europe : 75.41 (49.74 - 103.02)
- Eastern Mediterranean : 130.97 (87.38 - 179.78)

B) Annual percentage change in obesity-related age-standardised death rate



Annual percentage change in age-standardised death rate

- Europe : -0.56 (-1.05 to -0.07)
- Region of Americas : 0.17 (-0.21 to 0.55)
- Western Pacific : 1.72 (1.30 to 2.15)
- Africa : 0.02 (-0.13 to 0.17)
- Eastern Mediterranean : 0.90 (0.79 to 1.02)
- South-East Asia : 1.76 (1.44 to 2.08)

Figure 4

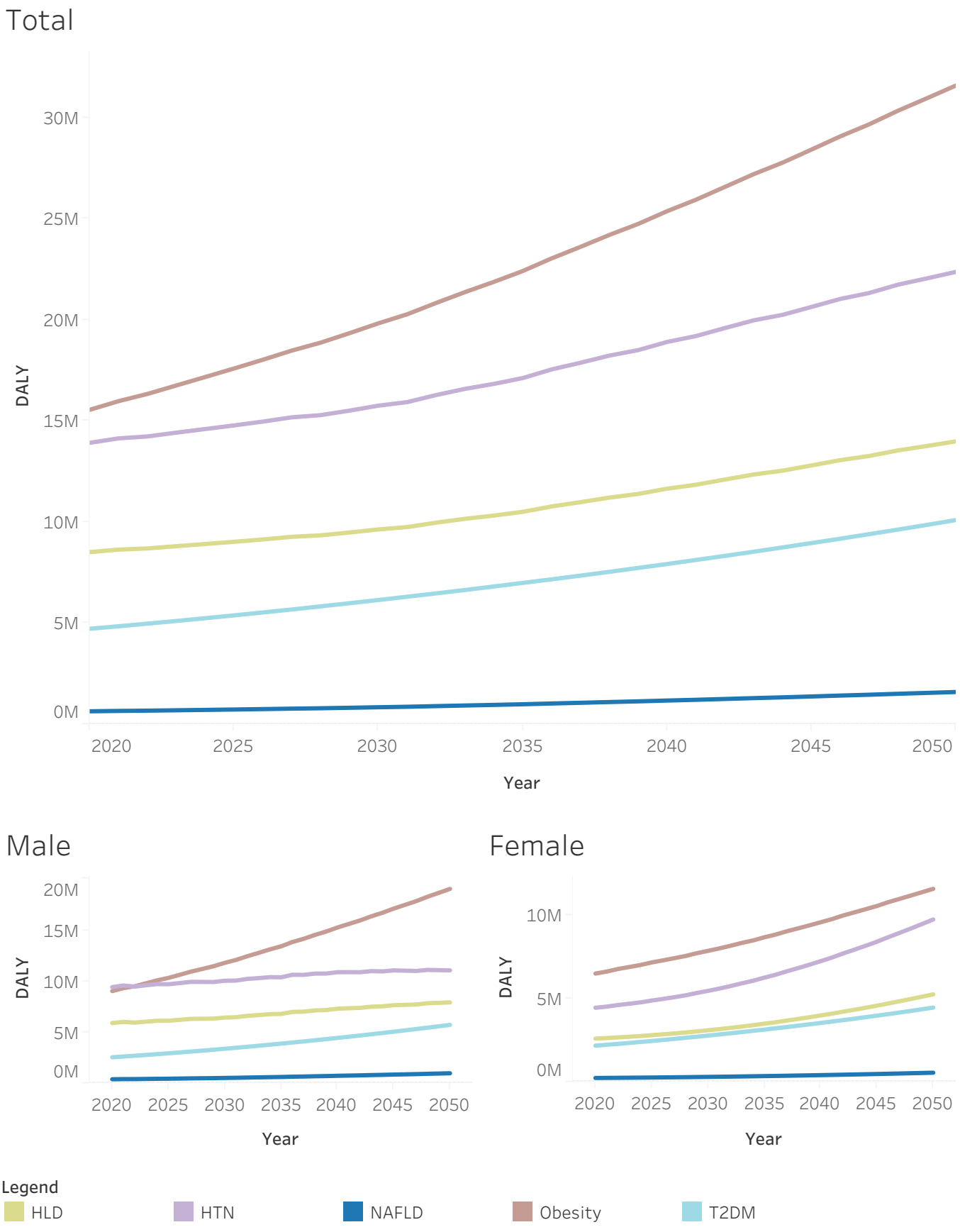
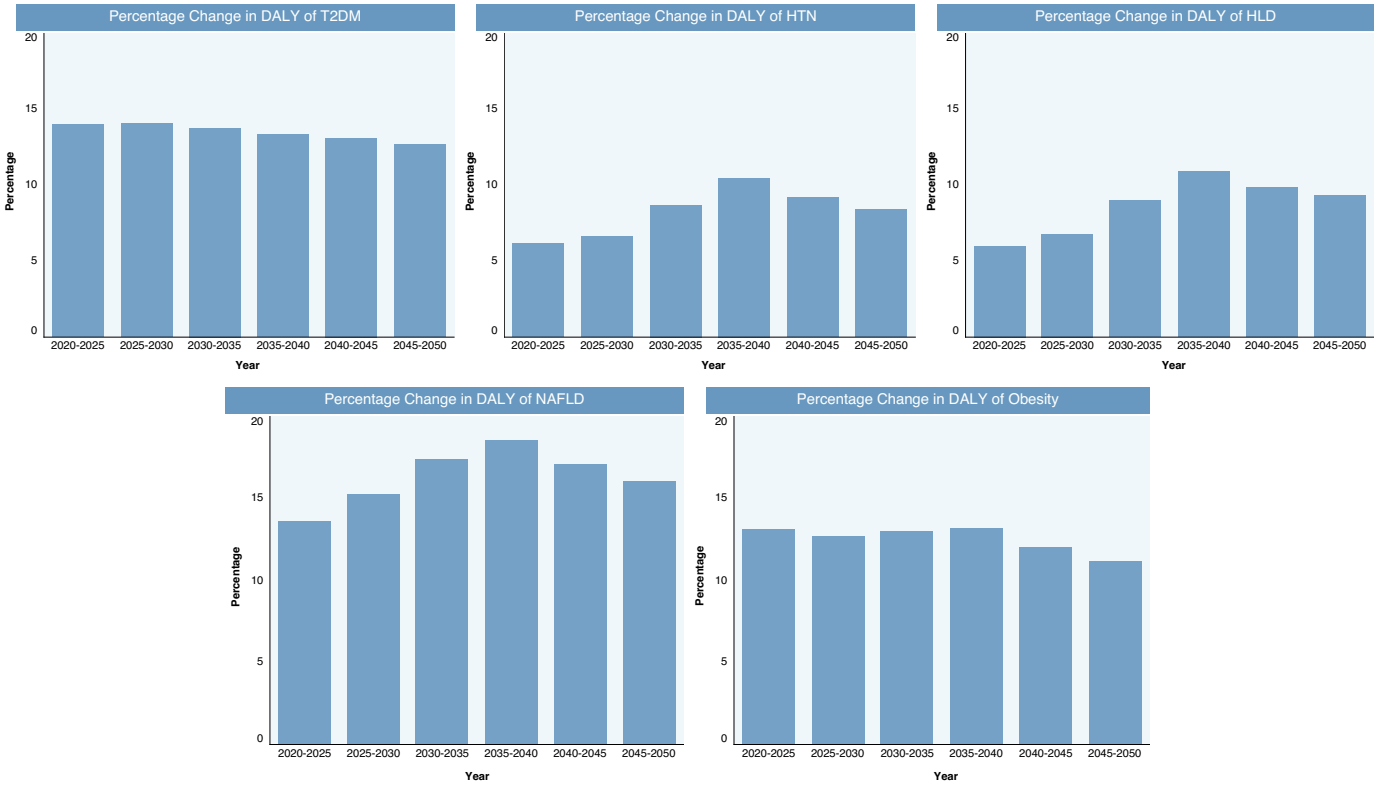


Figure 5



METABOLISM-D-22-01813R1
Title: The Global Syndemic of Metabolic Diseases in the Young Adult Population: A Consortium of Trends and Projections from the Global Burden of Disease 2000-2019
Metabolism

Dear Editor and Reviewers,

We would like to thank you for reading our manuscript ID METABOLISM-D-22-01813R1, entitled "*The Global Syndemic of Metabolic Diseases in the Young Adult Population: A Consortium of Trends and Projections from the Global Burden of Disease 2000-2019*" and providing insightful comments. We implemented your suggestions and they substantially improved the manuscript. Where possible, we have highlighted our changes in the revised manuscript and supporting information in red font.

Below we present point-by-point responses to reviewers' comments together with the actions we have taken in the paper to address these comments. For better tracking, the comments are shown in regular font and our responses are shown in red and italics.

Dear Dr. Chew,

Your manuscript entitled "The Global Syndemic of Metabolic Diseases in the Young Adult Population: A Consortium of Trends and Projections from the Global Burden of Disease 2000-2019" has again been carefully reviewed by the Editorial Board
of Metabolism. Basically the revision is now acceptable for publication, but before final acceptance is given, I would appreciate it if you would address the remaining issues raised by the reviewer(s).

If you are willing to do this, it would not be necessary for me to return the manuscript to the reviewer(s), but it could then be accepted for publication. I am returning to you the comments from the reviewer(s), which I hope you find helpful. If you are willing to revise the manuscript further, please return to me the new revision as well as a cover letter indicating each change you have made in response to a comment by the reviewer(s) by Jan 25, 2023. Please copy and paste each and every reviewer's comment above your response. While you are again free to provide rebuttal in your covering letter, I would prefer that you address the concerns in the manuscript.

We would like to extend our sincerest gratitude to the Editorial team for the constructive feedback on the manuscript. We have revised the manuscript according to your kind recommendations and hope that the manuscript can now be considered for publication.

I realize that you have spent a great deal of time and effort revising the manuscript, but feel these additional points should be addressed.

Please ensure that the manuscript source file you upload is provided in an editable format, e.g. Microsoft Word or LaTeX. If your paper is accepted for publication, an editable file is required for typesetting purposes.

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https://www.elsevier.com/authors/author-services/data-visualization to find out about available data visualization options and how to include them with your article.

Sincerely yours,

Christos Mantzoros, MD DSc PhD h.c.
Editor-in-Chief, Metabolism, Clinical and Experimental Professor of Medicine, Harvard Medical School

Editors and Reviewers' comments:

Editors:

Certain authors may have some concerns about studies derived from the Global Burden of Disease registry; can you please be proactive and address in a sentence or two?

We will like to extend our gratitude to the Editor for pointing this out. We believe that this is an important point to address and we have included this in the Strengths and Limitations section. the GBD 2019 study is one of the most comprehensive worldwide databases of diseases and has been utilised by various policy-makers globally to direct public health policy. The GBD has made several comprehensive efforts to ensure accurate GBD estimates, accountability, comparability of measurement, and generalisability (1). In our study, we have included the complete data estimates derived from the GBD 2019 study, thus allowing the findings to represent the broader populations *(Pages 17-18, Lines 432-437)*

Reference

1. Murray CJL. The Global Burden of Disease Study at 30 years. Nat Med. 2022;28(10):2019-2026.

The manuscript is well written and balanced. After the successful revision, the manuscript has been improved and the authors' point of view is better highlighted. Some differences with existing literature are adequately discussed.

There are some minor issues, including the formatting of highlights that are not formatted according to the journal guides, and some typos, which, however, could be corrected.

Thank you. We have checked and corrected the formatting of the highlights and typos in the paper.

Reviewer #1: All my comments have been satisfactorily addressed

We thank the Reviewer for the feedback.

Reviewer #2: -

Metabolism has implemented a new set of guidelines for authors. Please refer to these guidelines at http://www.metabolismjournal.com/authorinfo and format your manuscript accordingly. Only manuscripts that are in the proper format are considered. Please make sure acknowledgements, funding info, conflicts of interest, contributions of authors are added at the end of manuscript.

Thank you, we have formatted the manuscript accordingly.

Please also perform an updated literature search and cite any relevant papers recently published in Metabolism or elsewhere.

Thank you, we have added the important update of references and included papers recently published in Metabolism.

References as numbered in manuscript

[29] Sun DQ, Jin Y, Wang TY, Zheng KI, Rios RS, Zhang HY, et al. MAFLD and risk of CKD. Metabolism. 2021;115:154433.
[30] Mantovani A, Zaza G, Byrne CD, Lonardo A, Zoppini G, Bonora E, et al. Nonalcoholic fatty liver disease increases risk of incident chronic kidney disease: A systematic review and meta-analysis. Metabolism. 2018;79:64-76.
[46] DeMarsilis A, Reddy N, Boutari C, Filippaios A, Sternthal E, Katsiki N, et al. Pharmacotherapy of type 2 diabetes: An update and future directions. Metabolism. 2022;137:155332.
[48] Huangfu G, Jaltotage B, Pang J, Lan NSR, Abraham A, Otto J, et al. Hepatic fat as a novel marker for high-risk coronary atherosclerotic plaque features in familial hypercholesterolaemia. Metabolism. 2023;139:155370.

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We thank the Reviewer for this suggestion. The authors have thoroughly read through the manuscript and ensured that all grammatical errors have been addressed.

Please scrutinize statistics, data presentation and include a paragraph with strengths / weaknesses las well as a summary of the translational potential of the messages in the paper.

Thank you. We have scrutinised the statistics, data presentation and ensured that all study findings were accurate.

We have added important points in the Strengths and Limitations section within the Discussion as follows, "This study takes advantage of the 'Global Metabolic Syndemic' framework and compares the trends of all metabolic diseases in the young adult population, stratified based on sex, geographical regions and socioeconomic standing. The findings are important in informing policymaking strategies with the projection of the global metabolic burden up to 2050. Moreover, the GBD 2019 study is one of the most comprehensive worldwide databases of diseases and has been utilised by various policy-makers globally to direct public health policy. The GBD has made several comprehensive efforts to *ensure accurate GBD estimates, accountability, comparability of measurement, and generalisability [10]. In our study, we have included the complete data estimates derived from the GBD 2019 study, thus allowing the findings to represent the broader populations [10]. However, this study is not without its limitations." (Lines 429-438, Pages 17-18)*

The authors have also added a summary of the translational potential that is important and in line with the message of the manuscript: "The integration of population health and biomedical sciences through the strategic partnerships between researchers, clinicians and policymakers can facilitate the implementation of novel translational discoveries into clinical practice. With the pursuit of the first US Food and Drug Administration (FDA)-approved NAFLD therapeutics in the pipeline, now being evaluated in late-stage clinical trials, future translational studies are warranted to explore the additional metabolic effects of these therapeutics (namely peroxisome proliferator-activated receptor agonists, GLP1-RA) on the overall metabolic milieu such as insulin sensitivity, de-novo lipogenesis, and weight reduction [25, 60]. The enthusiasm for discovering novel therapeutics and their benefits on metabolic health is ever-increasing but should maintain the importance of lifestyle modifications and optimisation of cardiovascular comorbidities." (Lines 465-474, Page 19)

We thank the Editor and Reviewers for the constructive feedback. We hope the paper is now suitable for publication in *Metabolism*. Please let us know if there are further areas that need improvement. Thank you!

Best Regards,
Professor Mamas A Mamas
Dr Nicholas WS Chew
Department of Cardiology, National University Heart Centre, National University Health System, Singapore

Checklist of information that should be included in new reports of global health estimates

Item #	Checklist item	Reported on page #
Objectives and funding		
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.	6
2	List the funding sources for the work.	3
Data Inputs		
For all data inputs from multiple sources that are synthesized as part of the study:		
3	Describe how the data were identified and how the data were accessed.	7-8
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.	7-8
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	7-8
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	17-18
For data inputs that contribute to the analysis but were not synthesized as part of the study:		
7	Describe and give sources for any other data inputs.	NA
For all data inputs:		
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	NA
Data analysis		
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	7-8
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	7-8
11	Describe how candidate models were evaluated and how the final model(s) were selected.	NA
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	NA
13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	7-8
14	State how analytic or statistical source code used to generate estimates can be accessed.	NA
Results and Discussion		
15	Provide published estimates in a file format from which data can be efficiently extracted.	Tables
16	Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).	9-13
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	15-19
18	Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.	17-18

This checklist should be used in conjunction with the GATHER statement and Explanation and Elaboration document, found on gather-statement.org

Credit Author Statement

Bryan Chong: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Software, Validation, Writing - original draft, review & editing

Gwyneth Kong: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Software, Validation, Writing - original draft, review & editing

Kannan Shankar: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Software, Validation, Writing - original draft, review & editing

HS Jocelyn Chew: Investigation, Data curation, Formal analysis, Software, Validation, Writing - review & editing

Chaoxing Lin: Investigation, Data curation, Formal analysis, Software, Validation, Writing - review & editing

Rachel Goh: Investigation, Data curation, Formal analysis, Software, Validation Writing - review & editing

Yip Han Chin: Investigation, Data curation, Formal analysis, Software, Validation Writing - review & editing

Darren Jun Hao Tan: Validation, Writing - review & editing

Kai En Chan: Validation, Writing - review & editing

Wen Hui Lim: Validation, Writing - review & editing

Nicholas Syn: Investigation, Data curation, Formal analysis, Software, Supervision, Validation, Writing - review & editing

Siew Pang Chan: Investigation, Data curation, Formal analysis, Software, Supervision, Validation Writing - review & editing

Jiong-Wei Wang: Formal analysis, Software, Supervision, Validation, Writing - review & editing

Chin Meng Khoo: Formal analysis, Software, Supervision, Validation, Writing - review & editing

Georgios K Dimitriadis: Formal analysis, Software, Supervision, Validation, Writing - review & editing

Karn Wijarnpreecha: Formal analysis, Software, Supervision, Validation, Writing - review & editing

Arun Sanyal: Formal analysis, Software, Supervision, Validation, Writing - review & editing

Mazen Noureddin: Formal analysis, Software, Supervision, Validation Writing - review & editing

Mohammad Shadab Siddiqui: Formal analysis, Software Supervision, Validation, Writing - review & editing

Roger Foo: Conceptualization, Methodology, Formal analysis, Software Supervision, Validation, Writing - review & editing

Anurag Mehta: Conceptualization, Methodology, Formal analysis, Software Supervision, Validation, Writing - review & editing

Gemma Figtree: Supervision, Validation, Writing - review & editing

Derek J Hausenloy: Conceptualization, Methodology, Formal analysis, Software Supervision, Validation, Writing - review & editing

Mark Y Chan: Conceptualization, Methodology, Formal analysis, Software Supervision, Validation, Writing - review & editing

Cheng Han Ng: Conceptualization, Methodology, Investigation, Data curation Formal analysis, Software, Supervision, Validation, Writing - review & editing

Mark Muthiah: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Software, Supervision, Validation, Writing - review & editing

Mamas A Mamas: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Software, Supervision, Validation, Writing - review & editing

Nicholas WS Chew: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Software, Supervision, Validation, Writing - original draft, review & editing