Measuring the burden of comorbidity for ischaemic heart disease and four common non-communicable diseases in Iran, 1990–2017: a modelling study based on global burden of diseases data

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ABSTRACT
Objective This modelling study aimed to estimate the comorbidity burden for four common non-communicable diseases with ischaemic heart diseases (IHD) in Iran during a period of 28 years.

Design Analysis of the burden of comorbidity with IHD based on data included prevalence rates and the disability weight (DW) average for calculating years lived with disability (YLDs) from the Iran population based on the Global Burden of Disease (GBD) study.

Setting Population-based available data in GBD 2017 study of Iran population.

Participant The source of data was the GBD 2017 Study. We evaluated IHD, major depressive disorder (MDD), diabetes mellitus (DM), ischaemic stroke (IS), and osteoarthritis (OA) age-standardised prevalence rates and their DW.

Main outcome measures A new formula that modified the GBD calculator was used to measure the comorbidity YLDs. In the new formula, some multipliers were considered, measuring the departure from independence.

Result The contribution of total comorbidity for each combination of IHD with DM, MDD, IS and OA was 2.5%, 2.0%, 1.6% and 2.9%, respectively. The highest YLD rates were observed for IHD_MDD, 16.5 in 1990 and 17.0 in 2017. This was followed by IHD_DM, from 11.5 to 16.9 per 100 000. The YLD rates for IHD_OA changed slightly (6.5–6.7) per 100 000, whereas there was a gradual reduction in the trends of IHD-IS, from 4.0–4.5 per 100 000.

Conclusion Of the four comorbidities studied, the highest burden was due to the coexistence of MDD with IHD. Our results highlight the importance of addressing the burden of comorbidities when studying the burden of IHD or any other non-communicable disease.

INTRODUCTION
Cardiovascular disease (CVD) is the leading cause of death worldwide. About 17.9 million people passed from CVDs in 2019, representing 32% of all global deaths. According to the World Health Report, the impact of CVD will continue to increase in all regions of the world, with ischaemic heart disease (IHD) accounting for 9 million deaths in 2017. In Iran, mortality due to IHD is lower than in Central Asia or Eastern Europe, but higher than in Western Europe or East Asia. The Global Burden Disease (GBD) study reported 42.4% of all deaths in Iran were related to CVD in 2017, among which almost 59.6% were due to IHD. Therefore, more attention is being drawn to IHD burden in Iran in recent years.

Extensive studies have been carried out to identify the clinical course of IHD, its risk factors, methods of prevention and treatment. It is well established that IHD may co-occur with other conditions independently or with conditions related to its presence. Comorbidities can influence the prognosis, progression of the disease, clinical outcomes, treatment response, patient compliance, secondary prevention and healthcare costs.
in IHD patients. For example, according to the World Health Survey, the co-occurrence of depression with other chronic diseases tends to cause significantly more disability and disease burden compared with having either chronic disease alone.\(^6\) Such synergistic effects have been shown in the literature.\(^7\) The opposite (antagonistic effect) is also possible. However, few longitudinal studies have evaluated the burden of comorbidities and these studies mostly considered treatment characteristics or comorbidity progression over a short period of time.\(^8\)\(^9\)

Among prevalent non-communicable diseases that may co-occur with IHD more often than expected by chance are major depressive disorder (MDD), diabetes mellitus (DM), ischaemic stroke (IS) and osteoarthritis (OA). We selected these diseases because of their high prevalence and high probability of co-occurrence with IHD.

The burden of comorbidity is the impact of health problems caused by co-occurring diseases and their consequences as measured by financial cost, mortality, morbidity or other indicators.\(^10\)\(^11\) We have defined the burden of comorbid conditions as the burden caused by a disease that may occur with IHD, such as MDD, DM, IS and OA which is the reason of why we considered disability as a priority of this paper. In addition, we did not find an acceptable estimation for the YLL of comorbidities, even in the database of the GBD study. Therefore, we examined our concept only with the disability component of the burden of disease.

According to our definition, the years lived with disability (YLDs) due to comorbidity is caused by the existence of both diseases at the same time, and YLDs due to each comorbid condition is YLD that is only caused by one of the diseases, such as MDD, DM, IS and OA.

Depression is considered an IHD risk factor as well as one of its consequences. Depression is a widespread and debilitating mental illness that can be diagnosed and treated. In Iran, depression is considered among major public health challenges and constitutes 35%–45% of mental disorders.\(^12\) The prevalence of depression among CVD patients varies from 20% to 30%, depending on the evaluation method, clinical status, disease severity and sex.\(^13\) DM due to comorbidity is another disease that increases the risk of CVD and especially IHD.\(^14\) The risk of death due to heart disease in patients with DM is increased in both sexes. Data show that the prevalence of IHD is relatively high among patients with type II DM in Iran.\(^15\)

IHD can be accompanied by an elevated risk of IS.\(^16\) IHD and IS share many risk factors, such as high LDL and low HDL cholesterol levels, hypertension, smoking, DM, physical inactivity and being overweight or obese. IS in patients with acute coronary syndrome is twice as common as those without it.\(^17\)

There is some evidence that OA is associated with CVD, although the precise nature of this relationship has not been fully elucidated.\(^18\) A study on 7000 patients over 15 years showed that the mortality rate is 40% higher due to IHD in men with OA in each finger joint than those who did not have OA. A recent study suggested that the increased risk of CVD may be partly due to the use of non-steroidal anti-inflammatory drugs (NSAIDs), whose association with CVD is well established.\(^19\)\(^20\)

The burden of IHD and other chronic conditions in Iran has been estimated by the GBD.\(^20\) GBD estimates of non-fatal (disability) burden for each condition are adjusted for the presence of comorbidities.\(^20\) However, GBD did not have the estimation of burden due to comorbidity. The purpose of the current study was to estimate the disability burden due to comorbidity, defined as the co-occurrence of IHD with each of the four aforementioned conditions including, DM, MDD, OA and IS in Iran.

**METHODS**

**Data Source**

We used data from the Global Health Data Exchange website created by the GBD group update 2017 [https://gbd2017.healthdata.org/gbd-search](https://gbd2017.healthdata.org/gbd-search)\(^4\)\(^5\). Non-fatal disease burden was estimated in terms of YLDs, defined as disease prevalence × disability weight (DW). We obtained data for prevalence and average DW for each disease that were calculated by taking YLDs divided by prevalence for each disease based on the GBD website information. The age-standardised disease prevalence rates in both sex per 100 000 for IHD, DM, MDD, IS and OA, were extracted for Iran for the years 1990, 2000, 2010 and 2017, which all this information is available in the aforementioned GBD website. We did not consider age-specific or sex-specific rates. Since we did not know the distribution of severity levels for all disease sequelae in Iran, we used an approximate average DW for each disease, calculated as comorbidity-adjusted and age-adjusted YLDs divided by disease prevalence.

**Calculating YLDs for comorbidity**

In estimating non-fatal disease burden due to comorbidity, it is important to consider two assumptions that underlie GBD burden estimates. The first assumption is that the diseases occur independently. Under the independence assumption, the expected prevalence of comorbidity equals the product of the age-standardised prevalence of each disease. GBD uses a microsimulation model to estimate the co-occurrence of all conditions and their sequelae.\(^21\) The second assumption is that disability in persons with multiple diseases can be calculated from the DWs for each condition by a standard multiplicative formula.\(^20\)

As a basic calculation of the YLD of each disease, the prevalence rate multiplied by the DW. Correspondingly, determination of the YLDs due to comorbidity are formed on the same basis, with the difference that the effects of two diseases at the same time are considered in DWs and prevalence, which is discussed in detail below.

In the primary analysis, we followed the GBD approach by assuming independence for calculating prevalence and
multiplicativity when calculating DWs for persons with multiple conditions. However, despite being common in the literature, both assumptions may not be justifiable for many combinations of diseases. For example, different diseases may be causally related to each other, have common risk factors and/or interact in their effect on disability. Therefore, in a sensitivity analysis, we relaxed these assumptions in the following way.

To evaluate departures from independence in estimating the prevalence of comorbidity, we defined both multiplier, denoted by \( \rho \), through which the correlation between two diseases can be captured. For example, if \( \rho = 2.0 \), prevalence of comorbidity is twice that expected by chance. We used an analogous approach when evaluating the effects of departures from the assumption of multiplicative effects (no interaction on the multiplicative scale) of diseases on comorbidity-related disability. We modified the DWs in persons with more than one disease by applying a multiplier (denoted as \( \beta \)) to each individual DW, as named DWc in equation (1).

\[
DW_c = DW_1 \times \beta_1 + DW_2 \times \beta_2 - DW_1 \times \beta_1 + DW_2 \times \beta_2
\]

Accordingly, if \( P_1 \) and \( P_2 \) denote prevalence of each disease, the general formula for calculating total YLDs for two diseases in the presence of comorbidity can be written as:

\[
YLD = (P_1 - P_1 \times P_2 \times \rho) \times DW_1 + (P_2 - P_1 \times P_2 \times \rho) \times DW_2 + P_1 \times P_2 \times \rho \times DW_c
\]

(2)

The first two parts of equation 2 are the contributions of each individual disease and the third part is the contribution of comorbidity. The multipliers \((\beta_1, \beta_2, \rho)\) can be seen as measures of departure from independence and multiplicativity. In the absence of correlation and interaction between two diseases, the multipliers would equal 1. They would be greater than 1 in case of positive correlation/interaction and lower than 1 in case of negative correlation/interaction.\(^{22}\) Assuming independence of the two diseases and a multiplicative model for disability (all multipliers equal 1.0), the formula performs similarly to the standard approach used by GBD.

It should be clear from equations (1) and (2) that there is a linear relationship between each multiplier and comorbidity YLDs. If \( \rho \) is 0, there is no overlap between the two diseases and the comorbidity burden is 0. If one of the \( \beta \)s is 0, DWc equals the DW for the other condition. The multipliers need to be constrained such that neither DWc nor prevalence of comorbidity exceeds 1. In this calculation, we added this flexibility in our sensitivity analysis that \( \beta_1, \beta_2, \rho \) changes between 0.2 and 5, which means the risk of the second disease in the presence of the first one decreases or increases up to five times (online supplemental appendix 1, tables 1–3).

**Patient and public involvement**

No patient involved.

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**Table 1** Age-standardised prevalence per 1000 and disability weights for the conditions studied; Iran, 2017

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Prevalence per 1000</th>
<th>Disability weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>18.8</td>
<td>0.043 (0.032_0.054)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>74.3</td>
<td>0.081 (0.06_0.1)</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>38.5</td>
<td>0.201 (0.158_0.244)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>49.0</td>
<td>0.031 (0.018_0.055)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>17.3</td>
<td>0.153 (0.12_0.179)</td>
</tr>
</tbody>
</table>

Based on the GBD data.

GBD, Global Burden of Disease.

**RESULTS**

**The burden due to comorbidity**

DWs and the prevalence of each disease in 2017 are shown in table 1. Prevalence ranged from 17.3 per 100 000 for IS to 74.3 per 100 000 for DM. MDD had the highest DW \((0.201)\), followed by stroke \((0.153)\), DM \((0.081)\), IHD \((0.043)\) and OA \((0.031)\).

In figure 1, for each pair of conditions, we show the per cent contribution of each disease alone and their combination (comorbidity) to YLD burden, under the assumptions of independence and multiplicativity. In the year 2017, comorbidity accounted for 2.5% of YLDs for the IHD_DM combination, 2.0% for IHD_MDD, 2.9% for IHD_OA and 1.6% for IHD_IS.

Trends in comorbidity-related YLD rates for Iran in 1990–2017 are presented in figure 2 and table 2. Rates were fairly stable for all disease pairs except IHD_DM. The highest rates were observed for IHD_MDD, 16.5 per 100 000 in 1990 and 17.0 per 100 000 in 2017. For IHD_DM, YLDs increased by 47%, from 11.5 per 100 000 in 1990 to 16.9 per 100 000 in 2017.
Trend analysis shows that comorbidity-related YLD rates for IHD_MDD and IHD_DM have increased significantly during the 4 years with the p values of 0.031, 0.048, respectively. While IHD_OA and IHD_IS have not shown a significant change during these years (p values are 0.544, 0.212 respectively).

**Sensitivity analyses**

The results of sensitivity analyses are presented graphically in **figure 3**. Comorbidity YLDs increased linearly and proportionally to ρ (prevalence) **figure 3A**. The results were a little more complicated for the β₁ and β₂ multipliers. For each unit increase in β₁, the increase in comorbidity YLDs was a function of both conditions’ prevalence and DWs. When we increased β₁ (multiplier for IHD), the slope was steepest for IHD_DM, followed by IHD_OA and IHD_MDD (**figure 3B**). However, IHD-MDD had the highest intercept. YLDs increased by 5.5 per unit for DM, 2.5 for MDD, 3.8 for OA and 0.8 for IS. When we increased β₂ (multiplier for the comorbid condition), the slope was highest for IHD_MDD (13.9), followed by IHD_DM (10.9), and was relatively low for IHD_IS (3.1) and IHD_OA (2.8) (**figure 3C**, online supplemental appendix tables 1–3).

**Figure 2**  Trends in YLDs due to comorbidity for MD, MDD, OA and IS with IHD in Iran, 1990–2017. DM, diabetes mellitus; IHD, ischaemic heart disease; IS, ischaemic stroke; MDD, major depressive disorder; OA, osteoarthritis; YLD, years lived with disability.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>YLDs due to IHD alone</th>
<th>YLDs due to each comorbid condition</th>
<th>YLDs due to comorbidity</th>
<th>% YLDs due to comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD and DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>82.2 (61.2_103.2)</td>
<td>381.3 (282.4_470.7)</td>
<td>11.5 (8.6_15.1)</td>
<td>2.4</td>
</tr>
<tr>
<td>2000</td>
<td>80 (59.5_100.5)</td>
<td>392.2 (290.5_484.2)</td>
<td>11.9 (8.9_15.7)</td>
<td>2.5</td>
</tr>
<tr>
<td>2010</td>
<td>76.5 (56.9_96.1)</td>
<td>482.9 (357.7_596.2)</td>
<td>14.4 (10.8_19)</td>
<td>2.5</td>
</tr>
<tr>
<td>2017</td>
<td>74.7 (55.6_93.8)</td>
<td>593.4 (439.6_732.6)</td>
<td>16.9 (12.7_22.3)</td>
<td>2.5</td>
</tr>
<tr>
<td>IHD and MDD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>83.3 (62_104.6)</td>
<td>691.6 (543.6_839.6)</td>
<td>16.5 (11.5_18.3)</td>
<td>2.1</td>
</tr>
<tr>
<td>2000</td>
<td>81.2 (60.4_102)</td>
<td>701.8 (551.7_851.9)</td>
<td>16.8 (11.7_18.6)</td>
<td>2.1</td>
</tr>
<tr>
<td>2010</td>
<td>78.5 (58.4_98.6)</td>
<td>711.5 (559.3_863.7)</td>
<td>16.9 (11.7_18.7)</td>
<td>2.1</td>
</tr>
<tr>
<td>2017</td>
<td>77.6 (57.7_97.5)</td>
<td>760.6 (597.9_923.3)</td>
<td>17 (11.8_18.9)</td>
<td>2</td>
</tr>
<tr>
<td>IHD and OA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>82.5 (61.4_103.6)</td>
<td>137.6 (79.9_244.1)</td>
<td>6.5 (2.9_7.1)</td>
<td>2.9</td>
</tr>
<tr>
<td>2000</td>
<td>80.2 (59.7_100.7)</td>
<td>146.5 (85.1_259.9)</td>
<td>6.9 (3.1_7.5)</td>
<td>2.9</td>
</tr>
<tr>
<td>2010</td>
<td>77.3 (57.5_97.1)</td>
<td>158.1 (91.8_280.5)</td>
<td>7.3 (3.3_8)</td>
<td>3</td>
</tr>
<tr>
<td>2017</td>
<td>76.7 (57.1_96.3)</td>
<td>151.1 (87.7_268.1)</td>
<td>6.7 (3.7)</td>
<td>2.9</td>
</tr>
<tr>
<td>IHD and IS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>85.3 (63.5_107.1)</td>
<td>177.6 (139.3_208.9)</td>
<td>4.5 (3.5_5.1)</td>
<td>1.7</td>
</tr>
<tr>
<td>2000</td>
<td>83.3 (62_104.6)</td>
<td>157.1 (123.2_184.8)</td>
<td>4 (2.7_4.5)</td>
<td>1.6</td>
</tr>
<tr>
<td>2010</td>
<td>80.6 (60_101.2)</td>
<td>161.5 (126.7_190)</td>
<td>4.1 (2.7_4.6)</td>
<td>1.6</td>
</tr>
<tr>
<td>2017</td>
<td>79.8 (59.4_100.2)</td>
<td>170.1 (133.4_200.1)</td>
<td>4 (2.7_4.5)</td>
<td>1.6</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; IHD, ischaemic heart disease; IS, ischaemic stroke; MDD, major depressive disorder; OA, osteoarthritis; YLDs, years lived with disability.
The purpose of this study was to determine the burden of comorbidity in Iran attributed to IHD and one of four common concurrent diseases, namely MDD, DM, IS or OA. With the ageing of the population, the likelihood of comorbidity increases\(^ {25} \) and there is a need for valid methods to calculate the burden of comorbidity to assist the healthcare systems in setting priorities for management, prevention and control.\(^ {24} \)

Calculating the burden of comorbidity has not been explicitly addressed in the literature, and for most chronic diseases, including IHD, information on the burden of comorbidity is limited. Most studies have been conducted in selected populations over a short period of time and without considering various combinations of diseases that may coexist.\(^ {25} \) We believe this is an important subject to address, given the increasing role of comorbidity as a determinant of population health.

The contribution of comorbidity to the overall disease burden depends on the prevalence of both conditions and their DWs. In our study, the proportion of YLDs due to comorbidity was highest for the IHD_OA combination, followed by IHD_DM. Trends in burden due to comorbidity depend on the trends in the prevalence of both conditions since DWs are assumed to be constant. Our analysis shows the highest burden for IHD_MDD. This is not too surprising given the high DW for MDD and its relatively high prevalence.\(^ {20} \) However, the burden due to IHD_DM increased the most over the past 28 years and has now reached a level almost equal to that of IHD_MDD. Moreover, although the DW for IS is higher than the DW for DM, its lower prevalence has led to lower YLDs for IHD_IS in comparison to IHD_DM.

Depression is more common in women than in men.\(^ {26} \) Over the past decade, the evolution of women’s participation in society has led to a decline in the prevalence of mental disorders such as MDD.\(^ {27} \) Also, for more than two decades, the mental health programme in Iran has been expanded to the primary healthcare system and rural areas. Medical services for mental disorders, including MDD, have been available to the general population since 2005.\(^ {27} \) However, MDD has risen in prevalence in recent years. One postulation is that urbanisation and economic problems have contributed to this rise in prevalence. Further investigation is needed to determine the reasons for the increase in MDD prevalence.\(^ {28} \)

Insufficient physical activity, poor nutrition and obesity are common risk factors for DM.\(^ {29} \) As a result, the prevalence of DM has been increasing since 2000, especially in Eastern Mediterranean region.\(^ {30} \) Prevention of IHD in DM and choosing recommended treatments for cardiovascular disorders is a major challenge. Given the rapid increase in the prevalence of DM in recent years and the fact that the survival of patients with IHD in most parts of the world has increased, we will have more patients suffering from comorbidity of these two diseases in the future. Increasing obesity is also the most likely cause of a rise in OA prevalence since 1990, although OA prevalence has declined to some extent in recent years.\(^ {37} \)

Over the past two decades, we have witnessed a decline in the prevalence of IS in Iran. Well-established factors shared between IHD and IS include hypertension, high blood glucose, high cholesterol, obesity, smoking and low physical activity.\(^ {32} \) Prevention of IS and IHD has been a priority for healthcare providers in Iran, and the declining trend follows a similar trend elsewhere.\(^ {33} \)

In this study, we calculated the burden of comorbidity under the assumptions of independence and multiplicative effect on disability. Under these assumptions, the contribution of comorbidity to disease burden for each pair of conditions studied is relatively small compared with the contribution of each disease alone. The main reason is that the probability of disease co-occurrence is very small for independent conditions whose prevalence is low. For example, for two conditions with a prevalence of 5%, only 0.25% of the population will have both conditions by chance. However, the prevalence of comorbidity would have been 25% for two uncorrelated conditions present in 50% of the population each.

Clinical experience and current evidence suggest that chronic conditions tend to cluster in the same patients more often than expected by chance.\(^ {34} \) For example, depression may be present in as many as 25% of patients with IHD.\(^ {35} \) According to a systematic review of Australian
studies, 60% of people with CVD had OA, 20% had DM and 10% had asthma or mental disorders.\(^{36}\) The frequent co-occurrence of chronic conditions can be due to causal relationships between them (eg, DM and IHD),\(^{14}\) possibly mediated by treatment side effects (eg, IHD in OA mediated by NSAIDs),\(^{37}\) or similar risk factors and/or biological mechanisms (eg, IHD and IS).\(^{32}\) For these reasons, for many pairs or combinations of diseases, the assumption of independence seems difficult to justify. Our sensitivity analysis shows that departures from independence (positive or negative correlation) may have a strong effect on the prevalence and, consequently, the contribution of comorbidity to total disease burden.

Another major assumption in our calculations is using a multiplicative utility model for calculating DWs in people with comorbidity. Although this model is common in the literature and is supported by previous studies,\(^{38}\)\(^{39}\) its universality across all disease combinations is questionable. In fact, there are data to suggest that diseases may interact both synergistically and antagonistically in their impact on symptoms, function and quality of life.\(^{22}\)\(^{36}\) These interactions affect DWs of both diseases and should be considered in the calculations of comorbidity burden.\(^{43}\) For example, the interaction between IHD and DM may put patients at higher risk of physical disability than expected for the individual effects of each disease.\(^{40}\) Effects on physical disability were found for combinations of OA with IHD, pulmonary disease and obesity, whereas OA seemed to dampen the effect of hypertension on disability.\(^{18}\)\(^{42}\)

In our sensitivity analysis, we allowed DWs for disease pairs to vary to demonstrate the impact of such interactions on disease burden. It should be noted that the multiplicative model implies that the total burden of two or more conditions is negatively associated with the level of correlation between them. In other words, the more overlap there is between two conditions, the lower their total burden. Our sensitivity analysis shows that when interactions are allowed, the total burden can increase with increased overlap.

A limitation of our study is that we did not have access to real-life data on the simultaneous occurrence of multiple conditions in Iran. Since it is considered a specific DW for different severity of each disease, in this study, only the amount of DW that was used in the GBD website was considered for each disease. Moreover, we only considered comorbidities for a few selected pairs of diseases. The tables and graphs of this study were calculated and plotted based on the independence assumption of the two diseases. Since this formula has the flexibility to consider different dependencies in disease prevalence and DWs. It provides an opportunity for further study and research in estimating these coefficients for different comorbidities in future research. In this study, only an interval of (0.2–5)\(^{3}\) is considered as an example, just to show the formula changes to different coefficients and a sensitivity analysis. Co-occurrence of several health problems can have a negative impact on quality of life and the ability to work, as well as increase the risk of mortality.\(^{49}\) Finally, comorbidity is more common among older persons and may vary by sex. In this analysis, we used age-standardised data but did not address the effect of age or sex explicitly.

**Conclusion**

In conclusion, our results describe the burden of comorbidity over 28 years under the standard assumptions of independence and multiplicativity and demonstrate the potential impact of relaxing these assumptions. Of the four comorbidities studied, the highest burden was due to the coexistence of MDD with IHD. Our study highlights the importance of addressing the burden of comorbidities when measuring population health.

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**Contributors**

MM, KG and AH contributed equally in article writing, results and modelling, respectively. JAK was the article consultant for the results and modelling section. NS provided the main concept, conceived the article, took part in interpreting the results, revised all manuscript versions and guarantor for the overall content. SMSI contributed to the discussion, and commented on the manuscript. All authors read and approved the final manuscript.

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**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data availability statement**

Data are available in a public, open access repository.

Data used from the Global Health Data Exchange (GHDx) website created by the GBD group. The GBD website is categorised all the information based on sex, age, cause, Measure, location etc, and we based on the criteria of present study extracted the required information from the following website: https://gbd2017.healthdata.org/gbd-search.

**Supplemental material**

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