Author's response to reviews

Title: The burden of disease and injury in Iran 2003

Authors:

Mohsen Naghavi (drnaghavi@yahoo.com)
Farid Abolhassani (abolhassanif@tums.ac.ir)
Farshad Pourmalek (pourmalek_farshad@yahoo.com)
Maziar Moradi Lakeh (mmoradi@iums.ac.ir)
Nahid Jafari (nahidjafari_b@yahoo.com)
Sanaz Vaseghi (sanaz_v2001@yahoo.com)
Niloufar Mahdavi Hezaveh (nilou11@yahoo.com)
Hossein Kazemeini (kazemeini2001@yahoo.com)

Version: 2 Date: 3 March 2008

Author's response to reviews: see over
Description of revisions made to ‘The burden of disease and injury in Iran 2003’

Dear distinguished editor,

Please find below description of the revisions made to the manuscript 7772430156283491 “The burden of disease and injury in Iran 2003” along with its resubmission.

The paper will be edited by a fluent English writer immediately after kind consideration by the reviewers if you please (this was postponed because resubmission already took more than expected time due to unforeseen loss of files on correspondent author’s computer).

Thank you and best regards,
Farshad Pourmalek

Review 1

Reviewer's report
Title: The burden of disease and injury in Iran 2003
Version: 1 Date: 31 October 2007
Reviewer: Colin Mathers
Reviewer's report:

General

This paper presents results of a national burden of disease study for Iran in 2003. There is insufficient information summarizing the data and methods used for the estimation of mortality and YLD, or on revisions to the cause list and disability weights (see specific comments below). Summary results are presented for the attributable burden of 27 risk factors, but no information is provided in the paper on definitions of these risks, data or methods used. There are a large number of tables giving rankings of causes at various levels, but no tables presenting a complete set of estimates for all cause categories. For basic presentation of results, this is needed. The paper presents DALYs(3,1) but presents graphical comparisons with regional estimates of DALYs(3,0) These are not comparable. The presentation and discussion of results does not adequately summarize the pattern of burden of disease, with an excessive focus on quoting rankings of causes. The paper also needs substantial editing by a fluent English writer.

Provided more information summarizing the data and methods used for the estimation of mortality and YLD, and on revisions to the cause list and disability weights.

Totally omitted the burden of risk factors from the current manuscript.

Reduced the number and crowdedness of tables.

Provided a complete set of estimates for all cause categories (Additional file 1).

Omitted comparison of the results with DALYs(3,0).

Provided more accurate details for presentation and discussion of the results and removed the excessive focus on quoting rankings of causes.

---------------------------------------------------------------

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

P4. Is the title of the development plan "Law of the...." correctly translated? A reference to the original document should be provided. Also for those quoted in the Conclusions.
We confirm that the title of the ‘Law of the Fourth Economic, Social, and Cultural Development Plan of the Islamic Republic of Iran’ is correctly translated. A reference to the original document is provided (reference number 2), as well as to the book published on the study methodology and results (reference number 3). The reference for statements quoted in Conclusions is “Ministry of Health and Medical Education, Policy Making Council: The Comprehensive National Scientific Roadmap of I. R. Iran in Health Sector. Tehran; 2007.”, but we preferred to omit that part from the Conclusions (and hence, this reference).

P7. Methods. One sentence mentions that GIF was calculated for risk factors. No other details of the risk assessment are provided. If the paper is to include risk factor results, the methods section needs to include details of how risk factors were chosen, choice of counterfactuals, definitions, data sources for exposure and effect estimates etc, with references.

As advised, burden of risk factors is omitted from this manuscript.

P9. First para. The 5 “factors” cited in the deaths data collection description are vague and it is not clear what they mean in implementation, eg. how does the death data collection system “avoid assigning garbage codes”. The whole description of the deaths data system is vague and a much clearer description (and references) need to be provided. For example, how are “cemeteries” a source of deaths data?

Rewrote the whole description of death data system (page 13) and provided references (number 13-15).

P9 middle of page. Does this description of population data refer to population covered by the deaths data system specifically, or to the general population estimates. If the latter, needs to be moved to page 7. But unclear what this is about.

Sources of population estimates are for the death data system. Incorporated this point into the manuscript, with additional description of the source of death and population data for estimation of mortality rates (pages 12 and 14).

P9. Lower part of page. The 11 garbage codes need to be listed in a table together with a summary of how each was redistributed.

Listed the 11 garbage codes (table 1) together with a summary of how each was redistributed.

P9-10. The description of data inputs for the epidemiological assessments is insufficiently informative. A more systematic summary of data inputs and assumptions needs to be provided. For example:

• What infectious diseases were modelled from notifications systems. Which diseases were assumed to have 100% notification (not "near complete sensitivity"), and for those with less than 100%, what was assumed.

Surveillance system has complete sensitivity for a number of infectious diseases like polio, measles, and Crimean-Congo Hemorrhagic Fever. For others with incomplete sensitivity, like HIV, malaria, and tuberculosis, estimates of surveillance system sensitivity were used to find the actual number of cases. Estimates of sensitivity were used from international literature where available.
• Cancer registry. What does "covers the most prevalent cancers" mean? Does it not cover all sites of cancer? Does it cover the whole population, how complete is notification? A reference is needed.

Almost all sites of cancer are covered by the cancer registry system, which is primarily based on pathologic reports, and therefore does not give a good coverage for sites that are not routinely biopsied such as central nervous system, lung, pancreas, and some others. Given the incomplete coverage for some cancer cites, the following modeling approach was used for obtaining the epidemiologic estimates, using the specific mortality rates from both cancer registry and death registry in 2003, other sources of national and international information on cancer prevalence, incidence, and survival, and the Iranian clinicians’ judgment about survival settings of Iranian cancer patients.

Incidence and survival rates for cancer patients were obtained using the age-specific incidence rates estimated based on survival and mortality rates from cancer registry. The obtained incidence rates were used for calculation of incidence-to-mortality ratios and were also compared with incidence rates from cancer registry. If these incidence-to-mortality ratios were not compatible with rates deemed plausible for Iran’s setting, the survival rates were gradually changed to reach such plausibility. Survival information was fitted to a Weibull distribution for all ages. For calculation of the proportion surviving each specific cancer, a Weibull model was used as:

\[ S(t) = \alpha + (1 - \alpha) \exp\left[- \left( \frac{t}{\lambda} \right)^{\gamma} \right] \]

In which \(\alpha\) denotes proportion of those not dying from cancer, \(1 / \lambda\) is the time in which half of the patients will die, and \(\gamma\) is the shape parameter. Ten-year survival or S10 was used as the proportion not dying from cancer. The following formulas were also used in this model:

\[ \sigma_i = \frac{S_i - S10}{1 - S10} \]

\[ \sigma_s = \frac{S_s - S10}{1 - S10} \]

\[ \gamma = \ln \left( \frac{\ln \sigma_s}{\ln \sigma_i} \right) / \ln t \]

\[ \lambda = \left[ - \ln \sigma_i \right]^{\frac{1}{t}} \]

Different states that cancer patients may pass through (e.g. pre-metastatic or metastatic, untreated or treated, etc.) were used as described in the picture below. Using the data on proportion of patients undergoing treatment and those being cured, proportion of patients entering each state was calculated. Then using the incidence rate, number of patients entering each state was obtained. Using the average duration and disability weight of each state, YLD was calculated for all states and the results summed up for that specific cancer.
For assessing the internal validity of model for each cancer, the incidence rate obtained from model was checked against the incidence rate from cancer registry. Given the higher coverage of death registry as compared with cancer registry, the model was valid if the model-based incidence was higher than the cancer registry-based incidence (see sample figure below). Resultant burdens were also compared with burdens estimated for EMR-B and GBD for assessing the external validity of estimates.
A full description of the model used for cancers is planned to be presented in another manuscript.

• Hospital disease registries. Were these national, or a sample of hospitals? What was the data used? Admissions, or identified patients (ie. Only first episode for a patient counted).

Hospital registries were used for diseases that result in surgery, like inguinal hernia, cholecystitis, and gall bladder stones. In a number of provinces, hospital disease registries for such diseases have complete sensitivity. In provinces other than the Tehran province, 90% of hospitalizations occurred within the same province on average, resulting in a correction factor of 1.11. Average waiting time for emergency operations was 3 days (reference number 18).

• National epidemiology studies. A little more info on each of these is needed. Eg. what diseases covered, what was the study (a survey, self-report, ?, sample size etc)

All the national epidemiologic studies used had sample sizes and sampling methods resulting in samples representative of the national population. Moreover, sampling was also optimized to provide representative samples at the province level as well in a number of these studies. Most of these used structured interviews based on questionnaires, with clinical examination and paraclinical measurements where necessary, like anthropometric measurements, Decayed-Missing-Filled teeth, or blood and urine biochemistry. The main diseases in this category were mental and behavioral diseases including drug use disorders, malnutrition and micronutrient deficiencies including anemias, oral conditions, and some of the maternal and perinatal conditions. A table of studies, diseases and ICD codes, sampling, and data collection can be provided if still necessary.

• Injuries. Where did the durations come from? A summary table of these, plus disability weights would be very useful in understanding what was done. No need to mention that age weights and discounting were used for injuries, its already been said the study used DALY(3,1).

Durations of injuries and disability weights were adopted from GBD and Victorian BOD studies (references provided). Omitted the statement about the age weights and discounting.
Last sentence, YLD should be YLL.

Yes, this is correct. In response to the following comment by the reviewer 2,

Page 13, 1st para, last sentence: What was the reason for excluding accidents and injuries not leading to hospitalization and/or death? The GBD methods suggested using YLD-to-YLL ratios from relevant GBD region and multiply them with local YLL in the absence of emergency department data.

We corrected the text as follows: Accidents and injuries not leading to hospitalization but resulting in emergency department care or outpatient services were included. Only the trivial injuries managed by the injured persons without receiving any healthcare services were not included.

P13. Disability weights. A table should be provided for all disability weights, or at least for those that differ from those published for the GBD study. But particularly for the "new" causes, eg. acne.

Tables are provided for all disability weights (Additional file 2).

P15. I did not understand the description of how residual YLL were calculated. It would be helpful to have a table with the complete cause list used for the study. I refer to this again below. Were there not residual cause categories in each ICD chapter? If so, what does it mean to say there was a difference between YLL calculated from the deaths data and on the NBD list? I do not understand why a proportional algorithm would be used to assign deaths to the chapter-specific "other" categories. The size of these would depend on how many specific causes were included in the NBD list, not necessarily on the relative size of the cumulative deaths for those causes. Otherwise, the more specific causes that were included, the larger would be the residual category, whereas the opposite is what should happen.

Complete cause list used for the study is provided in additional file 1. There were residual cause categories in each ICD chapter, which were used to estimate the residual YLLs and then the residual YLDs. YLL calculated from the deaths data was higher than YLL calculated on the NBD list, since the former included all causes even the very rare ones not included in the latter. A proportional algorithm was used to assign deaths to the chapter-specific "other" categories, because the YLL calculated from the deaths data was higher than YLL calculated on the NBD list. As many specific causes as possible were included in the NBD list and in our cause list. This approach led to as low as possible the size of residual cause categories. For example, not all the cancers are used for estimation of YLL, but all cancers’ deaths are reflected in death registry data. Therefore, the cancer YLL calculated from death data were used for taking into account the deaths from cancers not included in the cause list. First, the residual YLL due to residual cancers was estimated, and then the residual YLD due to residual cancers was calculated.

P15. International comparisons. The EMR regional results for 2001 come from the Disease Control Priorities project, which did not use age-weighting. These results are not comparable with results using DALY(3,1) and should not be quoted or compared in this paper. The paper should use only EMR results from the latest GBD revision for 2002. It should not quote two separate sets of results for EMR for different years, as differences will mainly reflect differences in data inputs and methods.

Used only EMR results from the latest GBD revision for 2002.

P15. Results. The paper presents results only for YLL, YLD and DALYs. It needs to present mortality results (numbers of deaths by age sex and cause) also. The results tables do not
include a set of tables that list all causes in the study. This is important in providing a summary of the entire study. Tables giving ranks and top causes only are not adequate.

Mortality, YLL, YLD, and DALY for all causes along with their ICD codes are provided in Additional file 1, with breakdown by age groups, sex, and GBD and ICD classifications.

P16. Results are presented for various levels of cause groupings. But these are labelled in a number of ways as "ICD conditions", "ICD chapters", ICD entities. This is not very informative. The disease and injury causes should be listed in a Table with their ICD definitions. Note that the first and second level groupings do not always correspond to ICD chapters (unless the study revised the cause list to be an exact match: does not look as if this was done, but not possible to tell without the complete cause list). Refer to "disease and injury causes" or "detailed causes" rather than to "ICD entities". A number of the causes listed need either ICD code list, or preferably a brief explanation. For example, what does "addiction" cover: illicit drugs, prescription drugs, tobacco, gambling?

Provided the complete cause list with ICD-10 codes and groupings (Additional file 2). Referred to "disease and injury causes" or "detailed causes" rather than to "ICD entities". Preserved "condition" only for "perinatal conditions" and "maternal conditions".

Addiction refers to ICD-10 codes F11 (opioids) and F19 (multiple drug use and use of other psychoactive substances) and includes heroin and crack but does not include cocaine, cannabis, or prescription drugs (without concomitant use of opioids). Definitions and data are from 'The Epidemiological Study of Drug Abuse in Iran' [reference number 25: Yasami M, Shahmohammadi D, Naghavi M: Epidemiologic Study of Drug Abuse in Iran. Tehran: Ministry of Health and Medical Education; 2003] and were based on DSM-IV: about 1.4 million persons who had the 4 criteria of DSM-IV plus about 0.8 million persons who had been using these substances for more than one year but did not have the four DSM-IV criteria simultaneously. If needed, we will be glad to provide more details about addiction in this study.

Page 20. Depending how the attributions were done (not described), attributable burden usually cannot be added across risk factors. So results for risk factor burden as per cent of all risk factor burden should not be calculated or presented. The attributable burden of risk factors such as high blood pressure (2% of total) or smoking (0.6%) of total seem very low. The GBD CRA project estimated the attributable fractions for these two risk factors as 6% and 3% respectively for EMR-B. More information on data sources, estimated exposures and methods are needed, if the risk factor results are to be included.

As advised, burden of risk factors is omitted from this manuscript.

P34+ Tables. Format of tables showing rankings is very difficult to follow. Need to layout these tables more clearly. Suggest do not embed cause names among the numbers.

Took out the names embedded among the numbers.

Need to give tables for deaths, YLL, YLD and DALYS showing all causes. And a table or two giving details of age breakdown.

Mortality, YLL, YLD, and DALY for all causes along with their ICD codes are provided in Additional file 1, with breakdown by age groups, sex, and GBD and ICD classifications.

Figure 3. Uses labels "cluster III" etc not used elsewhere, and not explained. Would be useful to include some figures showing age-specific and cause-specific
rates as well as graphs showing proportions adding to 100%

Figure 3’s title and legend are provided in the main manuscript, page 37. We would like to such figures. In the meanwhile, we were provided with recommendation by the reviewer 2 to reduce the number of figures and tables and therefore we even omitted some of the previous tables and figures.

Figures 13+. The x-axis has age-ranges. The plots should be shown as bars, and not have continuous curves fitted to the data points.

We omitted figures 13+, in response to a recommendation by the reviewer 2 to reduce the number of figures and tables. However, figures 5 - 8 of American BOD study published in Population Health Metrics [Michaud CM, McKenna MT, Begg S, Tomijima N, Majmudar M, Bulzacchelli MT, Ebrahim S, Ezzati M, Salomon JA, Gaber Kreiser J, Hogan M, Murray CJ: The burden of disease and injury in the United States 1996. Popul Health Metr 2006;18(4):1] are exactly similar, with age ranges in the x-axis and continuous curves fitted to the data points.

Review 2

Reviewers’ report on "The burden of disease and injury in Iran 2003" by Mohsen Naghavi et al.

This review is reported by:
1. Hwee Pin PHUA, MSc (Statistics) Biostatistician, Epidemiology & Disease Control Division, Ministry of Health Singapore
2. Lily Ai Vee CHUA, MSc (Statistics) Statistician, Epidemiology & Disease Control Division, Ministry of Health Singapore
3. Stefan MA, CStat, PhD Acting Deputy Director (Biostatistics & Research), Epidemiology & Disease Control Division, Ministry of Health Singapore

The original Global Burden of Disease (GBD) Study initiated in 1992 was a joint collaboration by the Harvard School of Public Health, the World Bank and WHO. Since then, the WHO and a number of countries have adopted the GBD approach as the standard to assess healthcare system performance and guide rational resource allocation. The conduct of more national burden of disease studies and published findings using up-to-date demographic and epidemiological data will help facilitate international comparison. Good study such as this, conducted by the Iran team would be greatly welcome and encouraged.

For this paper, some suggestions and comments are listed as follows:

Major Compulsory Revisions

1. Insufficient details were provided on the methodology used in the estimation of burden attributable to selected risk factors. As current paper was already lengthy and mainly focusing on burden of disease findings, comparative risk assessment findings should be put in a separate paper incorporating a more detailed description of the methods employed. In this review, we had therefore commented solely on methods and findings of burden of disease in Iran.

As advised, burden of risk factors is omitted from this manuscript.
2. Page 3, 2nd para: “… templates for cancers and injuries, and adjustment for dependent comorbidity.” What were these adjustments for dependent comorbidity? Apparently, there was no mention of such adjustments in the Methods Section of the main paper, or were these adjustments referring to the comorbidity adjustments for injuries? Please clarify.

Adjustments for dependent comorbidity were for injuries, described in Methodology section under the subtitle ‘Injuries’.

3. Page 7, last para on “Population Estimation”: It would be better to provide more details on approach/modeling methods and to give relevant references if available.

Provided more details on population estimation approach (page 12).

4. Page 8, 3rd para: How complete were the data in the national death registry of MOHME or the 23 provinces for year 2003, and what were the techniques used to correct for underreporting of deaths if registration was found to be incomplete? In addition, as death registry of MOHME only covers part of the national population (23 out of the 30 provinces in 2003?), explain how the adjustments had been done to account for such underreporting of deaths.

1. Assumptions of population stability and no migration which are prerequisite for the Brass Growth-Balance and the Bennett-Horiuchi methods of death under-registration correction did not hold true for population of Iran (and their application albeit this fact, did not result in meaningful results). Described this in pages 15-16.

2. We corrected under-numeration in the death registration system with reference to deaths registered by the Civil Registration Organization of Iran. Described this in pages 15-16.

3. We described in page 27 that it should not be expected that rankings of the disease groups (by clusters of GBD or major disease groups) or even ranks of the most burdensome detailed causes within each disease group should be drastically sensitive to these assumptions.

5. Page 9, line 15: Please indicate which eleven garbage codes for causes of death were considered and briefly explain how each was treated in the cause of death analysis.

Listed the 11 garbage codes table 1 together with a summary of how each was redistributed.

6. Page 12, line 4: It was mentioned that 13,400 hospitalized trauma patients from 12 provinces were covered, how was this extrapolated to the whole nation, and in fact what was the coverage of hospitalization system in those 12 provinces?

The hospitalization system in those 12 provinces covered a population of 9.6 million. Assumptions for generalization of results from input data sample described above to the whole country population during the year were insignificance of YLD rates variability across the place and time.” That is to say the YLD calculated for the 4 months of the year 2003 covered by the study on 12 provinces can be generalized to the whole nation and to the whole year of 2003.

7. Pages 12 and 13 (Common DW): Please provide clearer explanation on the construction of the multiplicative model (and formula) and diagrams if available. In addition, how precise was this new method compared with the method used in GBD study? Any sensitivity analysis performed? It seemed that the two formulae of Common DW(3,1) and Common DW(2,1) did not correspond to each other. Besides, what would happen if all three co-morbidities have the
same duration? Were the formulas provided valid? Please see hypothetical and numerical example below:

- \(DW_1 = 0.725\) (spinal cord lesion) [Lifelong=LE]
- \(DW_2 = 0.35\) (fracture skull) [Lifelong, 15% incident cases]
- \(DW_3 = 0.064\) (nerve injuries) [Lifelong]

Common \(DW(3,1) = (0.064+(1-0.064)*0.35)+(1-((0.064+(1-0.064)*0.35)*0.725)))\)

= 1.108 (>1???)

Sensitivity analysis has not been performed yet to assess the precision of this new method compared with the method used in GBD study. Actually, the two formulae of Common \(DW(3,1)\) and Common \(DW(2,1)\) - as provided in the original manuscript - did not correspond to each other, due to a typing mistake in proper balance of parentheses. Therefore, the general formula of the multiplicative model was adopted from the references 1 and 5. If all three co-morbidities have the same duration, there would be only one common disability weight for the whole period.

Regarding the hypothetical and numerical example, the general formula of multiplicative model,

\[
\text{Common DW}_{(1,i)} = 1 - ((1-DW_1) \times (1-DW_2) \times \ldots \times (1-DW_i))
\]

Reduces to:

\[
\text{Common DW}_{(1,3)} = 1 - ((1-DW_1) \times (1-DW_2) \times (1-DW_3))
\]

And the calculations would read as:

\[
1 - ((1-0.725)(1-0.35)(1-0.064)) = 1 - (0.275 * 0.65 * 0.936) = 1 - 0.16731 = 0.83269
\]

As simple as when the common sensitivity of two parallel tests with sensitivities of 0.8 and 0.9 amounts to 0.98.

8. Tables and Figures: We felt that there were too many big tables and figures. Suggest authors to review whether some of the findings and corresponding tables or/and figures could be removed or refined to make the reporting as concise as possible. In addition, in order to aid readability, overcrowding tables and figures should be reduced or even avoided. Authors may wish to make reference to presentation formats adopted in some other published national burden of disease studies (e.g. Australia, South Africa, U.S.) for ideas. Alternatively, some of these tables and figures could have been moved to an appendix instead of be in the main paper.

Like other comments, this point is well taken as well and we modified all the tables to reduce complexity and increase readability. In addition, we omitted 2 tables and 5 figures to make the main paper more straightforward. Provided disability weights for all causes in the Additional file 2.

9. Page 22, last sentence: “… comparison of findings with burden of disease results of United States showed that the relatively heterogenous profile of health transition has still more way to advance toward a more homogeneous and developed state.” Firstly, heterogeneous was misspelt as heterogenous in the statement. Secondly, there was insufficient evidence provided in the paper to support this statement since only total DALY rates were compared between Iran and US (Figure 9). Suggest removing comparison with the US in paper or to include more details to justify statement made.

Removed comparison with the US throughout the paper (text, figures).
10. Please have a section to discuss briefly on study’s limitations.

A subtitle was given to the paragraph where the study limitations are discussed, that is "(D) Study Limitations and Innovations" under the Discussion and study limitation were explored in more detail. Provided more details on study assumptions and limitations. Similar subtitles were also highlighted under the Conclusions section.

11. Since the Iran NBD study team has modified the GBD list of diseases, please include the revised list with the corresponding ICD-10 codes in Appendix.

Mortality, YLL, YLD, and DALY for all causes along with their ICD codes are provided in Additional file 1, with breakdown by age groups, sex, and GBD and ICD classifications. Disability weights for all causes are provided in the Additional file 2.

Minor Essential Revisions

12. Throughout the paper, inconsistency in naming convention for disease categories and conditions (e.g. External causes = (?) Accidents & injuries = (?) Un-intentional and intentional injuries; Gastroenterology = (?) Gastrointestinal; Congenital = (?) Congenital and chromosomal, and etc) were observed. Please ensure consistent terminology used so as to avoid confusion.

Used nomenclature of ICD-10 consistently throughout the paper and provided all the ICD-10 codes in the Additional file 2.


Introduction section of the “NBD Guide” starts as follows: " The purpose of this manual is to provide clear practical advice to people undertaking national or sub-national burden of disease studies using the methods developed for the Global Burden of Disease (GBD) Study (Murray and Lopez 1996a). This manual is not intended to provide detailed conceptual or theoretical background to the development of the measures of population health used in burden of disease analyses, such as DALYs or the rationale for burden of disease studies. For such material, you should refer to the GBD publications, and other published papers on burden of disease analysis (see Section 1.5 below for references and information on where to obtain this material)."

The methods developed for NBD studies originated from the conceptual framework and methodology of the GBD. In the same time, a number of important modifications were
necessary for their applicability at the national level, and these very same alterations differentiate GBD from NBD studies. Please let us preserve our notion, if this can be affirmed.

14. Page 3, 3rd para, line 1: Please delete superscript “,” from the 100000 Iranian persons.

Done.

15. Page 3, 3rd para, lines 6-17: Suggest quoting in terms of % DALYs (total or male or female as deemed appropriate) instead of actual numbers.

As advised, quoted the mentioned values in percents from total DALYs.

16. Page 5, 1st para, line 7: Please briefly explain the choice of using these 6 provinces (out of the 30) in Iran in the study.

These 6 provinces were the provinces in which the Health Sector Reform (HSR) projects of MOHME supported by WHO and the World Bank in Iran were being implemented as pilot projects, to be extended to the whole country later. These provinces were chosen based on their prior capacities for organizational change in health sector and taking into consideration the fact that they should represent the provinces with relatively higher and lower levels of socio-economic and health development. National BOD was one of the HSR projects.

17. Page 5, 2nd para, line 3: Which were these 3 provinces?

The 3 provinces in which the preliminary study of Burden of Disease (BOD) was performed in 2002 were East Azerbaijan, Bushehr, and Charmahal & Bakhtiari.

18. Page 5, 2nd para, line -3: Suggest adding these words (in blue) “… social medicine practitioners, demographers, and clinical specialists with more than 10 collaborating…”

Modified as: “… demographers, and social medicine and clinical specialists …”, since social medicine is a medical specialty, but the word ‘practitioner’ may implicate a general medical degree not a specialty.

19. Page 7, 2nd para, line 1: Please change “NBD” to “GBD” and check the reference (*)
given in this review report for explanation.


Please see the response to comment number 13 above.

20. Page 7, 2nd para, line 3, “YLL(3,1), YLD(3,1) and DALY(3,1)”: It would be difficult for layperson to understand these notations. Would be good to briefly explain them and add relevant reference if available.

We modified the text as follows in order for the layperson to understand what is described.

We used the NBD methodology recommended by WHO to compute years of life lost due to premature mortality (YLL), years lived with disability (YLD), and disability-adjusted life years (DALY) and the GBD 1990 values of $C = 0.1658$ and $\beta = 0.04$. 

Page 12 of 18
were used for standard age weighting, and discount rate of $R = 0.03$ for health gain in future. C is an adjustment constant that ensures the equality of total burden with and without age weighting, $\beta$ determines the importance of age-weights, and R discount rate of adjusts for health gains or losses in the future [1].


21. Page 7, Method Section: Suggest re-organizing the order of the methods covered for better flow.

Specific departures from GBD methodology as highlighted in abstract and reiterated in Page Para 2 should come first (i.e. disease and injuries categories expansion, disability weights derivation, comorbidity adjustment for injuries and cancers burden estimation) followed by sections on population estimation, mortality estimation, epidemiological parameters estimation, residual estimation, and burden of disease management software.

Done.

22. Page 8, sub-section (Choosing the Diseases): State the exact numbers of disease and injury categories, and specific conditions considered in the study. Include appropriate reference for ICD-10.

Quoted the exact number of causes included in the study, which is 214, in the abstract and the main text (pages 12, 16, and 19). Included appropriate reference for ICD-10 (reference number 7).

23. Page 9, line 9: For readers who are not familiar with healthcare system in Iran, it would be better to describe what were those three levels of the health network system?

Description provided (page 13).

24. Page 10, 2nd para, line 5: Please list those most prevalent cancers covered in the Cancer Registry.

Almost all sites of cancer are covered by the cancer registry system, which is primarily based on pathologic reports, and therefore does not give a good coverage for sites that are not routinely biopsied such as central nervous system, lung, pancreas, and some others. Given the incomplete coverage for some cancer cites, a specific modeling approach described in the text was used for modeling cancers’ dynamics (more details on this model added to text, pages 8-9).

25. Page 11, line 2: Instead of using the word “etc”, suggest to use the phase [phrase] “and so on”.

Done.

26. Page 11, 1st para, line 3: To furnish more details on “CANMOD”. In addition, which years of data were used in the modeling?

Provided more details on “CANMOD” (pages 8-9). Data for year 2003 were used in the modeling.
27. Page 13, 1st para, last sentence: What was the reason for excluding accidents and injuries not leading to hospitalization and/or death? The GBD methods suggested using YLD-to-YLL ratios from relevant GBD region and multiply them with local YLL in the absence of emergency department data.

Corrected the text as follows: Accidents and injuries not leading to hospitalization but resulting in emergency department care or outpatient services were included. Only the trivial injuries managed by the injured persons without receiving any healthcare services were not included (page 11).


The above-mentioned sentence ("The age weights …") was omitted according to a comment by the Reviewer 1.


Quoted reference for the Delphi method used (reference number 13).

30. Page 16, line 1: “…5.53 years lost due to premature deaths…” The word million was missing.

The missing word 'million' was replaced.

31. Page 16, line 5: “ICD” should be “IDC”.

Changed "IDC-10" to "ICD-10".

32. Page 16, line 8: “(YLL plus YLD, absolute numbers)” is redundant which could be deleted.

Deleted the redundant part.

33. Page 16, line 8: 17 Chapters of ICD (presumably ICD-10) considered in Figure 1. What about the Chapter “Diseases of the ear and mastoid process”? Why was this not considered in Iran NBD disease classification list?

Deafness due to otitis media was modeled and its DALY calculated and presented along with DALY for upper respiratory infections.

34. Page 16: Suggest rephrasing ICD chapters to “major disease groupings”; ICD entities and ICD conditions to “specific disease conditions”. This suggestion should hold throughout the entire paper.

If you please, we followed Dr Colin Mathers' recommendation and used "ICD chapters" and "disease and injury causes" / "detailed causes" throughout the entire paper.

35. Page 17, line 3: One could not relate findings presented in this paragraph directly to Figure 4. Suggest changing Figure 4 to a horizontal bar chart presenting proportion of burden due to each major disease grouping by gender.
This paragraph is about comparison of the ranks of different major disease groups in males and females. Comparison of these ranks is depicted in Figure 4.

A horizontal bar chart presenting proportion of burden due to each major disease grouping by gender would be informative about the proportion of DALY due to each major disease group in males and females, not about the ranks and their comparisons.

36. Page 17, last para: Should it be ages 15-69 years instead of 15-70 years as indicated in line 1?

Changed 15-70 years to 15-69.

In addition, one could not relate some of the findings in terms of age group referenced to Figure 5 due to the age scale used. E.g.: “Females tolerated an extra burden of disability…. especially in 40-65 years of age” but this could not be observed from the figure presented.

The 40-65 age interval contains the highest proportion of the orange-colored shaded area, which represents the extra burden of disability in females as compared with males.

37. Page 18, 2nd para, 2nd sentence: Observed from Figure 7, it seemed that the age group should be 15-79 years and not 15-69 years.

Figure 7 dose now show the DALY rates (to which the sentence mentioned above refers). The DALY rates actually return to their at-birth values at age 60-69, as visible in the figure below (not used in the manuscript).

![Graph showing DALY rates by age and gender]

38. Page 18, 2nd para, 3rd sentence: Similar to above comment made, observed from Figure 7, it seemed that injuries accounted for the highest disability burden in those above 80 years and not those above 75 years.

It is correct that the injuries accounted for the highest disability burden in those above 80 years and not those above 75 years. Correction made in the manuscript.

This is because figure 7 shows the proportion of disability burden by the 3 major disease groups of GBD by age.
39. Page 18, sub-section (Burden by disease type and age): Suggest quoting the appropriate figures and/or tables immediately after the presentation of findings drawn from these illustrations. E.g., “Injuries accounted for the largest burden in those aged 5-44 years while non-communicable diseases was the leading cause of mortality burden in those aged 44 years and above (see Figure 6)”. To apply throughout the paper where appropriate.

   We applied this suggestion throughout the paper. This increases the readability. Thank you.

40. Page 19, line 1: Suggest changing the following phrases/word - burden of death to YLL; disability to YLD; total burden of death and disease/injury to DALYs.

   We omitted repetition of figures’ title in the main text (and used ‘see figure x’ instead), according to your previous comment. However, we applied your suggestion to the titles of the relevant figures (6-8).

41. Page 19, sub-section (International comparisons), 1st para: It would be more appropriate to compare based on age-standardized rate if data were available.

   Age-standardized rate if data were not available.

   For a fairer comparison, exclude the Bam earthquake (26 Dec 2003) in your comparison tables and charts.

   By ranking the natural disaster both with and without the Bam earthquake of December 2003, we know both the burden in year 2003, and the burden that is expected for next years without such and earthquake. Burden due to the Bam earthquake is not counted in the total burden, but it is provided in rankings, since it happened in 2003 anyway.

   Sufficient to compare with one year of data from the GBD for external validity checking. Use the most recent set for EMRO i.e. GBD 2002 estimates (source: http://www.who.int/healthinfo/bodgbd2002revised/en/index.html).

   Compared with year 2002 of data from the GBD for external validity checking.

   Convert Table 6 into a chart showing the differences in ranking of DALYs for EMRO 2002 and Iran NBD 2003 by broad GBD disease groupings.

   Omitted table 6 in response to comment number 44 above (reduction of tables and figures numbers).

   In addition, suggest removing Figures 12 to 16 as such detailed comparison by specific condition and age may not be meaningful since differences in estimates were likely due to differences in methodology and data sources.

   Removed those figures.

42. Page 19, sub-section (International comparisons), 2nd para: “Part of the differences in disease burden estimates for Iran 2003 and EMR 2000 and 2001 could be due to greater number of disease conditions in IRNBD study list”. Was this the main and valid reason? Please provide clarification on the reasoning given.

   We put in Discussion section under the ‘Regional Comparisons’ subtitle the 3 possible reasons as follows:
(A) Actual differences in mix of causes leading to differences in burden, (B), differences in sources of data and methodological details, like the greater number of disease and injury causes in IRNBD study list, and (C) chronological difference in reference year of calculations.

43. Page 20, sub-section (Risk factors): If the suggestion of removing findings on comparative risk assessment from the present paper is acceptable for the authors, then this sub-section is to be deleted eventually.

As advised, burden of risk factors is omitted from this manuscript.

44. Page 38, Table 3 (Ranking by YLL): Why were natural disasters (including Bam earthquake) – Rank 1, and natural disasters (excluding Bam earthquake) – Rank 20, both considered together?

Because the Bam earthquake of 2003 caused 28745 deaths out of the total 30032 deaths due to natural disasters, causing 936996 YLLs (or 95.68%) out of the total 979349 YLLs due to natural disasters, but such a huge disaster does not happen every year. By ranking the natural disaster both with and without the Bam earthquake of December 2003, we know both the burden in year 2003, and the burden that is expected for next years without such and earthquake. Burden due to the Bam earthquake is not counted in the total burden, but it is provided in rankings, since it happened in 2003 anyway.

However, we chose this table to omit in response to the comment number 44.

45. Page 43, Table 4, Rank 28 for females: It’s stated “Infertility (male and female)”. Please verify whether this is correct.

This is correct. Both the male and female fertility was calculated under females’ burden.

46. Page 45, Table 5: It may be sufficient to go by broad age groups e.g. 0-4, 5-14, 15-44, 45-64, 65-74, 75+

The 8 age groups used in the original table 5 were from GBD 2000 study. They were reduced to the 5 age groups of GBD 1990 study.

47. Figure 3: Should it be “% DALY” instead of “% DALY rate”?

It should not be “% DALY”, because the calculations are done for proportions of total all-cause both-sex DALY rates caused by each disease group in each sex.

48. Figure 5: There were 2 lines with the same circle symbol (when printed in black and white color), which may confuse the readers. Suggest using different symbol for one of the lines for clarity in case the figures were not printed in color.

Revised figure 5.

49. Figure 12: Missing y-axis title.

Revised figure 12.
Description of revisions made to ‘The burden of disease and injury in Iran 2003’

**Discretionary Revisions**

50. Pages 4-7, section (Background): Some texts, for example, 1st, last 2 paragraphs in this section are somewhat redundant, it would be good to rewrite this whole section.

The last paragraph of the Background section was omitted.

- Needs some language corrections before being published

The paper will be edited by a fluent English writer immediately after kind consideration by the reviewers if you please (this was postponed because resubmission already took more than expected time due to unforeseen loss of files on correspondent author’s computer).

---- The End ----