Author’s response to reviews

Title: Does economic development contribute to sex differences in ischaemic heart disease mortality? Hong Kong as a natural experiment using a case-control study

Authors:

C MARY Schooling (cms1@hkucc.hku.hk)
Tai Hing Lam (hrmrth@hkucc.hku.hk)
Sai Yin Ho (syho@hkusua.hku.hk)
Kwok Hang Mak (drkham@dh.gov.hk)
Gabriel M Leung (gmleung@hku.hk)

Version: 2 Date: 4 October 2007

Author’s response to reviews: see over
Dear Dr Zauner,

Thank you very much for your consideration of our manuscript; we were much encouraged by the reviewers’ very helpful and detailed suggestions to improve the paper, which we have incorporated in the present version.

Detailed responses to all the comments are below. Our responses are in italics, excerpts from the text are within quotes, new text is underlined.

Yours sincerely,

Mary Schooling

Reviewers's report

Title: Does economic development contribute to sex differences in ischaemic heart disease mortality? Hong Kong as a natural experiment using a case-control study
Version: 1 Date: 6 July 2007
Reviewer: Siegfried Geyer

Reviewer's report:
General

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

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

This is an interesting paper dealing with an important topic. The paper can be accepted for publication, the authors should complete the paper by providing some additional information: 1) The research question should be stated more clearly at the end of the introductory section.

We agree and have added a final sentence to the introduction stating our research question, as below.

“In the present study we examined whether the male excess risk of premature mortality from IHD, but not pneumonia, was higher with birth in an economically developed environment.”
2) Page 4, 1st paragraph: It is not clear how the data on demographic characteristics and health behaviours were collected. Please describe more precisely.

The sentence describing the data collection has been changed to include more information.

From:
“Information on demographic characteristics and health behaviours ten years previously of the decedent and a similar living person aged 60 years or older was collected from the person registering the death, who was usually one of the more educated adult children of the deceased’s family, often living in close, multi-generational Chinese families.”

To:
“Using a standardised questionnaire, information on current age, sex, place of birth and educational attainment and health behaviours (smoking, use of alcohol, dietary habits and leisure exercise), employment and housing ten years previously of the decedent and a similar living person aged 60 years or older was collected from the person registering the death, who was usually one of the more educated adult children of the deceased’s family, often living in close, multi-generational Chinese families.”

3) Page 5, last paragraph: Are the data on education, housing type and smoking status part of the survey or where did the data come from?

The potential confounders all came from the original survey. To make that clear we have added those words to the first sentence describing the potential confounders, as:

“Unconditional logistic regression adjusted for potential confounders (collected in the original survey) was used to assess the association of sex with IHD mortality by place of birth.”

4) The results presented in tables 2 and 3 are adjusted for socio-economic status and for lifestyle. It would be interesting to have the effects of these two in order to judge about the relative contribution of social differentiation as compared to migrant status (may be the effect of migrant status is secondary to socio-economic position).

We agree social differentiation could be another factor confounding the effect of migrant status. This is why we presented two models, firstly adjusted only for age and sex (model 1) and then additionally adjusted for socio-economic status and lifestyle (model 2). If social differentiation were making a major contribution to (or confounding) the observed relations, or if the effect of migrant status was secondary to socio-economic position, then any observed relations would be attenuated by adjustment for socio-economic status. However the reverse is the case (as shown in Table 2) suggesting that migrant men have a lower IHD mortality despite their socio-economic status and lifestyle. In fact, in this study as in previous studies in Hong Kong there is a fairly neutral relation between socio-economic status and IHD mortality. We have also previously reported the associations of smoking, second hand smoke exposure, diet and leisure exercise with mortality in this study, and we also have a paper concerning alcohol and mortality under
review. So, we would prefer to maintain the focus on migration and mortality in what is quite a complicated paper.

What next?: Accept after minor essential revisions

Reviewer's report
Title: Does economic development contribute to sex differences in ischaemic heart disease mortality? Hong Kong as a natural experiment using a case-control study
Version: 1 Date: 28 August 2007
Reviewer: Barbara Yawn
Reviewer's report:
General
This is an important topic and the natural experiment is a nice one to use. The division of ages at 74/75 is somewhat uncomfortable since this seems old. Most men have had an event by age 65 to 70 and the life expectancy of those in this age group is not 80 or 90. I would have been more comfortable with a cut at 64/65 or more justification of why cut later.

We chose 75 to be consistent with another study on this topic, and because Hong Kong has one of the longest life expectancies in the world. An age division at 65 gives a similar picture, although the difference between men and women born in Hong Kong is greater. We have changed the age division to 64/65 and changed the tables and any relevant text, i.e. in the statistical analysis section.

From:
“Consistent with other studies on sex differences in IHD mortality [2] and in view of the long life expectancy in Hong Kong, we classed death before 75 years as premature and so considered two age groups, 35-<75 years and 75 years or above.”

To:
“We classed death from IHD before 65 years as premature and so considered two age groups, 35-<65 years and 65 years or above.”

A nice discussion of why most of the other variables were used and why choices were made and why.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
The exact grouping of the data for use in the regression models is not entirely clear. The age adjustment categoriers need to be better defined as do other categories. Did you use a single term for age category? Is there linearity throughout the age categories.

Thank you for pointing this out, we have changed the sentence describing the potential confounders to give their categorization.
From:
“Potential confounders considered were age (in 5 year age-bands), education, housing type, smoking status, alcohol use, leisure exercise as categorised in Table 1 and the consumption of tea, dairy products, fish, meat, vegetables, fruit and soy more than 4 times a week or up to 3 times a week.”

To:
“Potential confounders considered were age (in 5 year age-groups), education (no formal, primary or secondary), housing type (hut/shared, public estate, self-owned or other), smoking status (never, ex-smoker or current smoker), alcohol use (ever or never), leisure exercise (less than once a month or at least once a month) and frequency of consumption of tea, dairy products, fish, meat, vegetables, fruit and soy (less than 4 times per week or at least 4 times per week).”

We also changed the footnotes to tables 2 and 3 to give these categorizations.

From:
“Model 2 adjusted for age (5 year groups), education, housing type, smoking, leisure exercise and alcohol use”

To:
“Model 2 adjusted for age (5 year groups), education (no formal, primary or secondary), housing type (hut/shared, public estate, self-owned or other), smoking (never, ex-smoker or current smoker), leisure exercise (less than once a month or at least once a month) and alcohol use (ever or never).”

We adjusted for age as a categorical variable in 5 year groups specifically to allow for a non-linear relation with age. Moreover, many in our population do not have birth certificates (because of the very history we are taking advantage of here) so their age is not exact and may be subject to digit preference. In these circumstances using age as a continuous variable would introduce error, which is avoided by using age as a categorical variable in age groups, with each age-group containing an age ending in 5 or 0.

Please justify why an unmatched analysis was chosen? To assure that this is of no concern could you stratify by age and show the results as confirming your current results?

Matched regression is something we thought of doing. Matched regression is often used in small case-control studies where there are insufficient observations to stratify by or adjust for confounders. However, we have a large study with a limited number of confounders, where we want to use the sample size and hence power to examine for effect modification by sex, which is not a very powerful test and requires a large sample.

Matched regression would mean we would not be able to use all our data and might not have the power to answer our research question. In addition, matched regression and regression adjusted for the same confounders should produce similar results.

As you suggested, we have re-run the analysis stratified by 10-year age groups, to avoid groups with no female deaths from IHD. There are relatively few deaths from IHD at younger ages, so the confidence intervals are quite wide. This analysis confirms your earlier insight that the age division should be at 64/65. In the younger age-groups Hong Kong born men are much more likely to die of IHD than Hong Kong born women, but
there is less difference after the age of 65. However, for people born in Guangdong there is no consistent sex difference across the age range. A graph illustrating this analysis is below.

Figure: Unadjusted odds ratio of IHD and pneumonia mortality in men compared with women by place of birth and 10 year age-group

![Graph showing odds ratios of IHD and pneumonia mortality by place of birth and age group.]

We have included this graph in the text, and changed the first two sentences of the second paragraph of the results accordingly.

From:
“Table 2 shows the odds ratios of dying from IHD or pneumonia in men compared with women stratified by birth-place and age-group, i.e. the reference group is women. Younger Hong Kong born men were significantly more likely to die from IHD than similar Hong Kong born women using either set of controls, adjusted for age (model 1) and also additionally adjusted for socio-economic status and lifestyle (model 2).”

To:
“Figure 1 shows the unadjusted odds ratios of dying from IHD or pneumonia in men compared with women by birth-place and 10 year age-group, i.e. the reference group is women. In the younger age-groups (35-44, 45-54 and 55-64 years) Hong Kong born men were about twice as likely to die of IHD than Hong Kong born women, however such differences were less clear for the Guangdong born or for deaths from pneumonia. Similarly Table 2 shows that younger (35 to 64 years) Hong Kong born men were significantly more likely to die from IHD than similar Hong Kong born women using either set of controls, adjusted for age (model 1) and also additionally adjusted for socio-economic status and lifestyle (model 2).”

Minors Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
The term on page 2 of "economic backwater" would not seem appropriate in a medical publication. "economically disadvantaged"???

We agree, we have changed the wording.

From:
“Guangdong province was an economic backwater until the establishment of the Special Economic Zones near Hong Kong in 1978”

“Economic development in Guangdong province was not a priority until the establishment of the Special Economic Zones near Hong Kong in 1978”

Discretionary Revisions (which the author can choose to ignore)

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Reviewer’s report**

**Title:** Does economic development contribute to sex differences in ischaemic heart disease mortality? Hong Kong as a natural experiment using a case-control study

**Version:** 1  **Date:** 6 September 2007

**Reviewer:** Per Wändell

**Reviewer’s report:**

**General**

This is an interesting article with the attempt to study gender differences in ischemic heart disease (IHD) in relation to economic development. The methods and statistics are well described and discussed, and the authors seem to be aware of possible limitations.

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

1. The background and discussion is far too brief.
   a) The context is actually migration and health, and there are many articles published on this issue. The authors should refer to relevant studies, i.e. changes in IHD incidence and mortality associated with migration to a higher economically developed country and region (e.g. the Honolulu Heart Study, but there are a great many studies), but also in changes in risk factors for IHD or description of risk factor profiles among immigrants. In general, studies usually find higher rates of overweight, obesity, metabolic syndrome, hypertension and diabetes.

   *Thank you very much for this suggestion. Migration from less developed to more developed countries provides a parallel to socio-economic development over historical time and a parallel to our study. We have added a section summarizing the findings and highlighting where our study fits.*

   “Migration from less to more economically developed countries provides a parallel with socio-economic development since the industrial revolution. Migration studies, such as the Honolulu Heart Study have been instrumental in understanding the trends in and environmental determinants of IHD. [5] Migration to more economically developed countries is usually associated with increased IHD risk, although, migration studies have not provided consistently converging scientific viewpoints.[6] The many different factors involved, i.e. ethnicity, country of origin and destination, acculturation, age at migration and generations since migration may all contribute to these disparate interpretations. [7-11] To our knowledge, no previous study has examined sex differences in IHD mortality with migration to a more economically developed location within an ethnically homogenous population.”
b) The authors have also written about the situation before economic development, i.e. in more traditional societies. They could refer to e.g., studies Melanesians in Kitava by Staffan Lindeberg, to get a baseline of the situation before Westernization of a society. When looking at blood lipids, there is no sign of reduced HDL-cholesterol among Swedish men in relation to women compared to the Kitava population.

Thank you very much for the reference to the fascinating, though small, study from Kitava. We have added a sentence providing a comparison of HDL-cholesterol levels between men and women in different countries.

“Moreover, sex-differences in HDL-cholesterol appear to be contextually specific and smallest in least developed locations, such as China, [35] suggesting they are environmentally driven, although these findings have not always been replicated in small studies. [36]”

c) When looking at life tables (accessible from the WHO), one could see small gender differences in e.g., some African countries, while in many other countries women have 3-6 years longer expected average length of life. This, however, seems to be mostly related to a high maternal mortality. When discussion gender differences in relation to economic development this is also a matter of possible importance.

We agree maternal mortality in childbirth does usually fall sharply with economic development, and this fall could be one of the reasons why gender differences in life expectancy change with economic development. Fewer women dying in childbirth would change the sex ratio in IHD mortality if the women who no longer die in childbirth are less likely than other women to die of IHD, whether this is the case or not is difficult to ascertain. However, in our study we are considering women who mainly spent their adult lives in Hong Kong, where maternal mortality is low and has been for many years. (Duthie SJ, Ghosh A, Ma HK: Maternal mortality in Hong Kong 1961-1985. Br J Obstet Gynaecol 1989, 96: 4-8.)

d) The authors could also discuss other risk factors, such as psycho-social stress associated with migration, as psycho-social factors were found to be of great importance in the INTERHEART Study.

Thank you for drawing our attention to this study. We agree psycho-social stress may be associated with migration, with associated impacts on the risk of acute myocardial infarction. We have added psycho-social stress as a possible explanation for our findings, with reference to the INTERHEART study.

“Alternatively, men and women may have responded differently to the stresses of migration and living in Hong Kong, with corresponding increases in IHD risk. [22] Although, stress has similar effects on IHD risk in men and women, [22] it is possible that life in Hong Kong was particularly stressful for migrant women and Hong Kong born men.”
2. Hypothesis.
a) The authors speculate that a better pre-adult environment increases sex-steroids at puberty, thus increasing gender differences. However, they hardly present any scientific support for this. When considering the studies mentioned above the authors should have discussed if their speculation could fit in with other studies. I doubt it.

Perhaps because of the difficulties of carrying out such experiments, most of the evidence that living conditions and particularly diet affect sex-steroids and/or pubertal development comes from animal experiments. To the 4 references concerning these animal experiments, we have added two more references concerning experiments in adolescents, and one study with observational evidence.

“Even in universally well-fed human populations, slight changes in diet affect sex-steroids in girls [39] although not in boys [40], where larger nutritional differences are needed [41].”

b) As regards diabetes, Gale found a tendency over time in Western societies from a female preponderance in the early 20th century to a more equal situation in the late 20th century. Possible explanations to that could be that men are more predisposed to central fat deposition, which also is associated with reduced oxidation of fat; this could predispose to higher incidence of IHD as well as of type 2 diabetes. Thus, another hypothesis is that men are more susceptible to environmental changes by economic development due to metabolic differences.

We agree completely that men may be more susceptible to the environmental changes associated with economic development due to metabolic differences, we are simply extending your hypothesis slightly by suggesting that men’s greater susceptibility arises at puberty. We also agree with you that diabetes is a counter-example, this is a point we thought about at length before submitting this paper. Finally we decided not to include anything about diabetes, firstly because we wanted to keep what is quite a complicated paper simple and focused and secondly because we could only discuss rather than test hypotheses about diabetes in this study, given that diabetes is a relatively rare cause of death.

In view of your observations about diabetes, we have now included diabetes in the discussion. Before, we wrote this paper, we reviewed the literature providing experimental or observational evidence on the factors affecting metabolic changes at puberty. Pubertal sex-steroids appeared to have sexually dimorphic effects mainly on lipids (particularly HDL-cholesterol) and body shape. On the other hand pubertal sex-steroids were less clearly related to pre-cursors of diabetes, which appear to be more strongly related to another hypothalamic-pituitary-endocrine axis, i.e. growth hormone. So, our tentative hypothesis that diet at puberty is driving levels of hormones and sex-steroids would imply that with the improvements in living conditions associated with economic development, there should be an increase in IHD in men compared with women, but not such a large change in the sex ratio for diabetes. Our hypothesis is still tentative and unproven so we would prefer to keep our discussion of it brief, and we have simply added one sentence covering this point.
“Moreover, consistent with the less marked change with economic development in the sex ratio for diabetes [20] than for IHD, such environmentally driven effects on pubertal sex-steroids would not be expected to affect pubertal pre-cursors of diabetes, which appear to be more strongly related to another hypothalamic-pituitary-endocrine axis, i.e. growth hormone. [44-49]”

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

The rate of IHD-deaths of all deaths is rather low. Thus, it is of value to show the greatest causes of death. Besides, the authors write that Hong Kong cause of death coding is found to be of good quality in other studies, but only one study is mentioned. This should be better supported.

*Hong Kong currently has a relatively low rate of IHD deaths, the greatest cause of death is cancer. We have added this information to the results.*

“Consistent with all deaths in Hong Kong in 1998,[28] the leading cause of death in the study was cancer (36%), followed by diseases of the circulatory system (27%) and respiratory system (20%).”

Data from death certificates is often used in research, however there are few studies anywhere which have taken a random sample of death certificates and checked these against autopsies performed for that purpose. Instead it is generally accepted that the causes of death provided on death certificates by trained doctors are valid and reliable. This is essentially the assumption we are making in this study, and in the many other studies using mortality statistics in Hong Kong and elsewhere. In Hong Kong, there is universal access to medical care and most people die in hospital. These hospitals are modern, publicly funded and staffed by highly trained physicians, who most likely have been treating the patient shortly before death. However, in this study and in any similar study using causes of death from death certificates we cannot rule out the possibility that some deaths are misclassified, which would make our results conservative. We have added that as a limitation.

“However, inevitably some deaths may be misclassified, which would make our results conservative”

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Discretionary Revisions (which the author can choose to ignore)

The heading to the tables is rather sparse, and thus it takes some time to understand the message of the tables. It would be easier for the readers if the authors proved the tables with more explaining heading text and in Table 1 also set some space between the age groups and between IHD and pneumonia cases. Besides, Tables 2 and 3 could be quicker read if the authors put in a parenthesis with (reference group, OR=1) after “women” and “migrants from Guangdong”, respectively, in the heading.
As suggested, we have changed the spacing in Table 1, and added the reference groups to the heading in Tables 2. Table 3 has the reference group explicitly shown in the table, as 1 against the row labeled “migrants from Guangdong”.

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests