PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between body mass index and onset of hypertension in diabetic and non-diabetic men and women: A cross-sectional study using national health data from the State of Kuwait in Arabian Peninsula
AUTHORS	Thangavel, Alphonse; Channanath, Arshad; Farran, Bassam; Behbehani, Kazem

VERSION 1 - REVIEW

REVIEWER	Jennifer Logue University of Glasgow UK
REVIEW RETURNED	04-Feb-2015

GENERAL COMMENTS	This paper examining association between BMI and age of onset of hypertension in patients with diabetes and without diabetes, and exploring sex specific differences is interesting. However the current presentation of the paper makes for very difficult reading and the results could be better presented in a more concise paper. Major comments: 1. What BMI measurement is used - registration, diagnosis of T2DM or diagnosis of hypertension? These all answer subtly different questions with important clinical implications so the choice should be clear throughout the paper and justified. 2. The presentation of results by giving the regression models is not reader-friendly at all. I suggest the presentation of the main results is reconsidered so it is far clearer to the reader what the results are. This should be in the abstract too. 3. English language needs review. 4. I do not understand the "variance of BMI" reported on page 10 ln 194 and 199. Is the within the individual? Does it suggest weight gain? 1.81kg/m2 of BMI is a significant weight change. 5. A flow chart for the selection of the patients from the data set would help

	Minor 1. I think you are probably looking at sex not gender differences

REVIEWER	Lucy Meoni The Johns Hopkins Bloomberg School of Public Health United States of America
REVIEW RETURNED	26-Feb-2015

GENERAL COMMENTS	The investigators used data from the Kuwait Health Network to test the hypotheses that, in people with hypertension, heavier weight is associated with younger age of onset of hypertension and that this relationship is stronger in persons with diabetes compared to those without and in men compared to women. A strength of this study is the wealth of data on a large number of persons under care and the repeated measures of weight and blood pressure, as well as other clinical information. The authors take an unusual approach in both study design and data analysis. First, everyone without hypertension is excluded, so the risk of developing of hypertension cannot be estimated—and the authors indicate that they are not interested in doing so. Although earlier onset of hypertension is not desirable, the added harm to a group who are all destined to develop hypertension is not clear. In addition, it is not a novel observation. People with diabetes are known to have an increased risk of hypertension and elevated blood pressure prior to and at the time of diagnosis of hypertension. For this reason, testing the hypothesis that diabetics have earlier onset of hypertension does not seem to add new knowledge and is not clinically important. Second, everyone who developed hypertension before the onset of diabetes is censored (excluded). Given that, for the reasons stated in the article, hypertension and diabetes are co-morbid conditions, this design feature creates a subset of persons with diabetes who are not representative of persons with diabetes. Third, persons who do not have repeated measures of body weight are excluded, even though it is not clear that repeated weight values are used in the analysis. Fourth, the approach of using linear regression is not optimal. Data are available in individuals prior to the development of hypertension and diabetes. A better approach is an analysis that includes all the members of the cohort with and without hypertension. One way to accomplish this is to use survival analysis with age at onset of hypertension as the outcome variable. This method would allow adjustment for covariates determined at registration time that are fixed, such as gender, as well as changes in covariates over follow up. Other comments The presumed biological mechanism for the proposed association of obesity with age at diagnosis needs to be clearer.

	The distribution of age and blood pressure at time of registration by diabetic status should be included in table one. In table 2A, the confidence interval for class 1 obesity for males and females appears to cross zero. How can the p value be significant?

VERSION 1 – AUTHOR RESPONSE

REFEREE 1: Jennifer Logue

1.1. This paper examining association between BMI and age of onset of hypertension in patients with diabetes and without diabetes, and exploring sex specific differences is interesting.

We thank the referee for finding the study interesting.

1.2. However the current presentation of the paper makes for very difficult reading and the results could be better presented in a more concise paper.

We worked through the manuscript to make it more concise – the actions include moving around the text to make a coherent reading, removing sentences that do not add much value, replacing certain texts with figures and tables, and splitting long sentences into simple sentences.

Two of our colleagues, who have good command of English usage, did extensive proofreading of the manuscript.

Major comments:

1.3. What BMI measurement is used - registration, diagnosis of T2DM or diagnosis of hypertension? These all answer subtly different questions with important clinical implications so the choice should be clear throughout the paper and justified.

BMI measurement at the time of diagnosis of hypertension is used in the study.

Text relating to this is seen in the manuscript under the methods section – "We evaluate associations between BMI and age at onset of hypertension by performing multiple linear regression analysis with age at onset of hypertension as dependent variable, and sex and BMI measurements (as measured at the time of hypertension diagnosis – see the Results section for justification on this choice) as independent variables." (page 8; lines 153-157).

Further, we have made this clear in the abstract by revising the sentence of Main outcome measures as below: "Main outcome measures Association between age at onset of hypertension and BMI (as measured at hypertension diagnosis)" (page 2; lines 43-44).

As regards the justification: We give the following text (pages 9-10; lines 191-208), in the revised ms, to address this comment and a related comment 1.6.

"The study considers only those patients who have been regularly monitored for BMI (at least every six months) over the period from the date of registration to the date of hypertension diagnosis. Average variance in BMI per individual, is seen to be low at 1.60 (data set of hypertension in diabetic patients) and 1.81 (data set of hypertension in non-diabetic patients). These observed average variances translate to variances of 4.36 Kg and 4.92 Kg in weight at the average height of 1.65 meters (average heights of Kuwaiti native men and women are 1.72 and 1.58 meters, respectively). This does not necessarily imply gain in weight in all the individuals; it just represents the dynamics in weight over the period from registration to onset of hypertension. Though the variance in terms of weight seems to be large, the variance in BMI does not necessarily mean transition into higher or

lower obesity class. The difference in these average variances in BMI between the two data sets is statistically insignificant (p=0.066). In order to reduce complexities arising due to the BMI dynamics while building the models, we consider the BMI measurements made at the time of hypertension diagnosis in our analysis. While it is required to consider the BMI taken at the time of registration in studies relating to prognosis models, consideration of BMI at time of onset in our study is in agreement with the practice seen in literature reports – for example, see [22]".

1.4. The presentation of results by giving the regression models is not reader-friendly at all. I suggest the presentation of the main results is reconsidered so it is far clearer to the reader what the results are. This should be in the abstract too.

We now present the regression equations in a table ("Table 2. Regression models, derived in this study, for age at onset of hypertension" see page 29) and restrict the relevant text in the results section to present just the findings from the regression equations.
We further improved the presentation of other main results – e.g. (i) We shortened the section on Descriptive Statistics by removing the text that just restates the data presented in the Table 1; (ii) we moved around text to make coherent and step-by-step presentation of the results.

As regards the results section in abstract, we rewrite it as below in the revised version of the ms (see page 2; lines 45-50):
"Results Age at onset of hypertension is inversely related to BMI; this relationship is seen stronger in men compared to women (slope estimate in men, -0.62 years per unit increase in BMI; in women -0.18) and in individuals (particularly women) with diabetes compared to those without (slope estimate in women, -0.39 versus -0.18, p<0.001; in men -0.66 versus -0.62; p=0.66). Being obese and diabetic while young (20-39 years) leads to severe risk of hypertension".

1.5. English language needs review.
We worked through the manuscript to make it more concise – the actions include moving around the text to make a coherent reading, removing sentences that do not add much value, replacing certain texts with figures and tables, and splitting long sentences into simple sentences.
Further, we got the revised ms reviewed by two of our colleagues who have better command in English usage.

1.6. I do not understand the "variance of BMI" reported on page 10 ln 194 and 199. Is the within the individual? Does it suggest weight gain? 1.81kg/m2 of BMI is a significant weight change.
Variance of BMI is calculated for every individual in the data set and then averaged over all the individuals in the data set. Thus, it is average variance per individual. This is made clear now in the manuscript. See Page 2; line 41. "Mean variance in BMI per individual over the period ---". Also see page 10; lines 193-194. "Average variance in BMI per individual, is seen to be low at 1.60 ---".
The difference in these average variances in BMI between the two data sets (i.e. between the variances of 1.60 Kg/m2 and 1.81 Kg/m2) is seen statistically insignificant. The above observed average variances of 1.60 and 1.81 Kg/m2 in BMI can translate to a difference of 4.36 Kg and 4.92 Kg in weight at the average height of 1.65 meters (average heights of Kuwaiti native males and females are 1.72 and 1.58 meters). This does not necessarily mean gain in weight in all the individuals; can be weight gain in some individuals and weight loss in some other individuals; it just represents the

dynamics in weight. Though the variance in terms of weight seems to be large, the variance in BMI does not necessarily mean transition into higher or lower obesity class.
The revised manuscript includes the following text. See pages 9-10; lines 191-203.
"The study considers only those patients who have been regularly monitored for BMI (at least every six months) over the period from the date of registration to the date of hypertension diagnosis. Average variance in BMI per individual, is seen to be low at 1.60 (data set of hypertension in diabetic patients) and 1.81 (data set of hypertension in non-diabetic patients). These observed average variances translate to variances of 4.36 Kg and 4.92 Kg in weight at the average height of 1.65 meters (average heights of Kuwaiti native men and women are 1.72 and 1.58 meters, respectively). This does not necessarily imply gain in weight in all the individuals; it just represents the dynamics in weight over the period from registration to onset of hypertension. Though the variance in terms of weight seems to be large, the variance in BMI does not necessarily mean transition into higher or lower obesity class. The difference in these average variances in BMI between the two data sets is statistically insignificant (p=0.066)".

1.7. A flow chart for the selection of the patients from the data set would help
We have now provided the suggested flowchart in the revised manuscript as "Figure 1. Flowchart for the methodologies used to carve out data sets used in this study". The flowchart is as below.

Minor

1.8. I think you are probably looking at sex not gender differences.
We have replaced all occurrences of "gender" to "sex" as well as "males/females" to "men/women".

REFEREE 2: Lucy Meoni
2.1. The investigators used data from the Kuwait Health Network to test the hypotheses that, in people with hypertension, heavier weight is associated with younger age of onset of hypertension and that this relationship is stronger in persons with diabetes compared to those without and in men compared to women. A strength of this study is the wealth of data on a large number of persons under care and the repeated measures of weight and blood pressure, as well as other clinical information.
We thank the referee for the notes on the strength of the study.

2.2. The authors take an unusual approach in both study design and data analysis. First, everyone without hypertension is excluded, so the risk of developing of hypertension cannot be estimated—and the authors indicate that they are not interested in doing so. Although earlier onset of hypertension is not desirable, the added harm to a group who are all destined to develop hypertension is not clear.
The objective of the study is to examine whether the relationships between onset age of hypertension and BMI are different in diabetic versus non-diabetic patients. As the outcome variable is onset age of hypertension; we excluded non-hypertensive patients. Inclusion of non-hypertensive

patients complicates the modeling of relationship between obesity levels and age at onset of hypertension. The added harm by diabetes to a group who are destined to develop hypertension is in terms of earlier onset of hypertension.

We now added results of analysis on Hazard ratios for developing hypertension in diabetic patients of increasingly obese categories which demonstrate the harm - the risk of developing hypertension in obese diabetic patients is at least 1.5 fold higher than that seen in normal weight non-diabetic individuals. See pages 15-17 lines 335-337; pages 14-15; lines 300-312 and also see the new Table 5. The newly added texts are as below:

"Enumeration of Cox proportional hazards in diabetic patients illustrates that being obese and diabetic brings in severe risk of hypertension to persons from younger age groups than those from advanced age groups".

"Hazard ratios for developing hypertension in diabetic patients of increasingly obese categories

We evaluate Cox proportional hazard ratios (HR) for developing hypertension in type 2 diabetic patients (against the baseline characteristics of normal weight and non-diabetic patients). The variability in hazard ratios in different categories of BMI are presented in Table 5. The results depict two major observations: (a) the risk of developing hypertension is at least 1.5 fold higher in obese diabetic patients; and (b) the risk associated with the age group of 20-39 is highest compared to the other two age groups. Higher BMI levels attribute to increased risk of developing hypertension in lower age groups than in higher age groups - for example, being severely obese (Class III obesity category) increases the hazard 4.5 fold in the age group of 20-39 years, as compared to an increase of only 1.7 fold in the age group of 40-59 and ≥ 60 years. There are no notable sex-specific differences in the hazard ratios".

2.3. In addition, it is not a novel observation. People with diabetes are known to have an increased risk of hypertension and elevated blood pressure prior to and at the time of diagnosis of hypertension. For this reason, testing the hypothesis that diabetics have earlier onset of hypertension does not seem to add new knowledge and is not clinically important.

It is known that obesity can induce hypertension that diabetes is a risk factor for hypertension, and that obesity acts differently in males and females. However, analyzing the interplay between the three factors of obesity, diabetes status, and gender in influencing the age at onset of hypertension is of interest and is adding new knowledge. Delineation of this interplay will help in developing further the current guidelines on hypertension prevention. The longer people can delay the onset of hypertension, the better off they are in terms of reducing lifetime risk of heart disease and stroke. Individuals who experience increases or decreases in BP in middle age have associated higher and lower remaining LTR for CVD (Allen et al, Circulation. 2012; 125: 37-44).

We have now added text summarizing the above paragraph in the revised manuscript. See page 17 lines 365-377. The relevant text is as reproduced below:

"Delaying the onset of hypertension reduces lifetime risk of heart disease and stroke. Individuals who experience increases in blood pressure during middle age have been associated with higher lifetime risk of cardiovascular disorders[16]. Clinical practice guidelines that help in prevention of hypertension present recommendations on dealing with the associated risk factors. The risk factors are at least of three types: (i) Modifiable risk factors such as obesity, diabetes, unhealthy diet, and low physical activity; (ii) Non-modifiable risk factors such as sex, family history, and ethnicity; and (iii) environmental risk factors such as low socioeconomic status and religious practices. Impact due to risk factors on onset of hypertension is exerted through a combinatorial interplay of factors of the

above three types. Delineation of this interplay, such as that reported in the current study (namely, the impact of interplay among BMI, sex, and pre-existence of diabetes on the age at onset of hypertension), will help in developing further the current guidelines on hypertension prevention and management".

2.4. Second, everyone who developed hypertension before the onset of diabetes is censored (excluded). Given that, for the reasons stated in the article, hypertension and diabetes are co-morbid conditions, this design feature creates a subset of persons with diabetes who are not representative of persons with diabetes.

As we are interested, in this study, to understand (& possibly quantify) how pre-existence of diabetes impacts the extent of correlation between BMI and age at onset of hypertension, we did not include patients who developed diabetes after the onset of hypertension. The referee points out that hypertension and diabetes are co-morbid conditions and hence suggests also using the subset of patients that develop diabetes after the onset of hypertension in the analysis.

We address this suggestion by considering a third data set as summarized in below. We have now added the following paragraph and figure in the revised manuscript. See page 13 lines 264-277 and online supplementary figure S3.

"Impact of obesity on age at onset of hypertension in patients destined to become diabetic

The analysis presented so far considers the impact of obesity on age at onset of hypertension in diabetic versus non-diabetic patients. As hypertension and diabetes are co-morbid conditions, it is desirable to examine the association of obesity on age at onset of hypertension in patients that are destined to become diabetic. For this purpose, we consider a third set of patients with onset of hypertension succeeding that of diabetes (see Figure 1). The characteristics of such a data set as compared with the other two data sets considered so far in the study are as depicted in online supplementary figure S3. The slope of the association of BMI with age at onset of hypertension (in the data set of diabetes onset after hypertension onset) is seen at -0.32 (see Table 2) which is of the same order as that observed with the data set of hypertension in diabetic patients".

2.5. Third, persons who do not have repeated measures of body weight are excluded, even though it is not clear that repeated weight values are used in the analysis.

One of the sanity checks that we do with the raw data is to make sure that the patients have been regularly monitored for onset of diabetes and hypertension – this ensures that the date of diagnosis is as close as possible to the date of onset. Records of repeated measures of BMI (along with others such as HbA1c and blood pressure readings) are an indication of regular monitoring. Further, we wanted to make sure that there is no large dynamics in the levels of BMI with the participants included in the study. See online Supplementary Information document page 4 lines 74-774.

Also see the answers to earlier queries 1.3 and 1.6.

2.6. Fourth, the approach of using linear regression is not optimal. Data are available in individuals prior to the development of hypertension and diabetes. A better approach is an analysis that includes all the members of the cohort with and without hypertension. One way to accomplish this is to use survival analysis with age at onset of hypertension as the outcome variable. This method would allow adjustment for covariates determined at registration time that are fixed, such as

gender, as well as changes in covariates over follow up.

As regards exclusion of non-hypertensive patients: as mentioned in reply to the query 2.4, the study deals with differences in age at onset of hypertension in response to BMI and presence/absence of pre-existing condition of diabetes. It is not the aim to evaluate the risk of developing hypertension per se.

We have not used survival analysis (to model the impact of pre-existence of diabetes on the correlation between age at onset of hypertension and BMI) as it usually quantifies time to a single dichotomous event while linear regression has its output variable as continuous. However, we had carried out Cox regression analysis to determine hazard ratios for developing hypertension in diabetic patients of increasingly obese categories against the baseline characteristics of non-diabetic normal weight categories. We now include this analysis and result in the revised manuscript. See pages 15-17 lines 335-337; pages 14-15; lines 300-312 and also see the new Table 5. The newly added texts are as below:

"Enumeration of Cox proportional hazards in diabetic patients illustrates that being obese and diabetic brings in severe risk of hypertension to persons from younger age groups than those from advanced age groups".

"Hazard ratios for developing hypertension in diabetic patients of increasingly obese categories

We evaluate Cox proportional hazard ratios (HR) for developing hypertension in type 2 diabetic patients (against the baseline characteristics of normal weight and non-diabetic patients). The variability in hazard ratios in different categories of BMI are presented in Table 5. The results depict two major observations: (a) the risk of developing hypertension is at least 1.5 fold higher in obese diabetic patients; and (b) the risk associated with the age group of 20-39 is highest compared to the other two age groups. Higher BMI levels attribute to increased risk of developing hypertension in lower age groups than in higher age groups - for example, being severely obese (Class III obesity category) increases the hazard 4.5 fold in the age group of 20-39 years, as compared to an increase of only 1.7 fold in the age group of 40-59 and ≥ 60 years. There are no notable sex-specific differences in the hazard ratios".

Table 5. BMI-wide and sex-specific differences in hazard ratios for developing hypertension in type 2 diabetic patients according to baseline diagnosis in non-diabetic & normal weight patients.

Age group BMI-wide differences in hazard ratios

Overweight category versus normal weight category Class I obesity category versus normal weight category Class II obesity category versus normal weight category Class III obesity category versus normal weight category

a. Both Men and Women (corrected for sex)

20-39 2.3*(0.69-7.51)

p=0.2 3.9(1.25-12.66)

p<0.05 3.8(1.17-12.25)

p<0.05 4.5(1.40-14.26)

p<0.05

40-59 1.3(1.08-1.55)

p<0.05 1.5(1.24-1.78)

p<0.001 1.6(1.34-1.95)
p<0.001 1.7(1.39-2.06)
p<0.001
60 and above 1.2(1.02-1.43)
p<0.05 1.5(1.22-1.73)
p<0.001 1.5(1.23-1.83)
p<0.001 1.7(1.32-2.11)
p<0.001
b. Men
40-59 1.3(1.05-1.68)
p<0.05 1.4(1.16-1.87)
p<0.01 1.5(1.17-1.99)
p<0.01 1.7(1.32-2.38)
p<0.001
60 and above 1.1*(0.92-1.45)
p=0.2 1.4(1.12-1.86)
p<0.01 1.3*(0.93-2.07)
p=0.1 1.8(1.10-3.18)
p<0.05
c. Women
40-59 1.2*(0.94-1.66)
p=0.13 1.4(1.12-1.96)
p<0.01 1.6(1.23-2.17)
p<0.001 1.6(1.24-2.21)
p<0.001
60 and above 1.2*(0.97-1.62)
p=0.07 1.4(1.16-1.91)
p<0.05 1.5(1.19-2.01)
p<0.01 1.6(1.24-2.24)
p<0.001

*, these values are not significant. p-value > 0.05.

Other comments

2.7. The presumed biological mechanism for the proposed association of obesity with age at diagnosis needs to be clearer.

We now have added the following paragraph in the revised manuscript: See page 5 lines 81-98. "Arterial hypertension is a chronic medical condition in which blood pressure in arteries is elevated. Blood pressure is generated when heart contracts against the resistance of blood vessels. Relationship between increasing age and hypertension prevalence has been illustrated[1,2]. The increase in blood pressure with age is associated mostly with structural changes (such as stiffness) in the arteries. Pathophysiological factors influencing onset of hypertension include impaired kidney

sodium excretion, altered renal and sodium metabolism, reset baroreflexes, reset local autoregulation responses, altered renin-aldosterone relationship, and increased responsiveness to sympathetic nervous system stimuli[3,4]. Obesity-induced hypertension, subject of this study, involves most often the above-mentioned factors (that mediate ageing-related hypertension). Obese individuals have increased fatty tissue which elevates vascular resistance and subsequently increases the workload on heart to pump blood. Obesity provides an impetus for sympathetic nervous system activation as well as for changes in renal structure and function. The arterial-pressure control mechanism of diuresis and natriuresis seems to be shifted toward higher blood-pressure levels in obese individuals. Leptin[5] and other neuropeptides are possible links between obesity and hypertension. Other mechanisms involved in obesity-induced hypertension are hyperinsulinemia and insulin induced sodium retention".

2.8. The distribution of age and blood pressure at time of registration by diabetic status should be included in table one.

We have now included these distributions in the revised manuscript. See Table 1 page 28; and page 9.

Hypertension in T2DM patients (n=3904) Hypertension in non-diabetic patients (n=1403) p-value@
Mean age at the time of registration 47.48 10.92 43.24 10.74 P<0.001

Mean Blood pressure values in mmHg at registration SP = 122.05 9.07
DP = 79.09 6.77
SP = 120.98 10.12
DP = 79.39 8.32 P<0.001
P=0.225

Page 9 line 186: "Mean age of the participants at the time of registration is around 45 10 years".

Page 9 lines 183-184: "Mean blood pressure values measured at onset of hypertension point to Stage 1 hypertension in both the data sets while those measured at the time of registration are normal".

2.9. In table 2A, the confidence interval for class 1 obesity for males and females appears to cross zero. How can the p value be significant?

This is a typo mistake. We forgot to type the negative sign. The text "(CI: -7.98 to 4.4)" should read as "(CI: -7.98 to -4.4)". This is incorporated in the revised manuscr

VERSION 2 – REVIEW

REVIEWER	Jennifer Logue University of Glasgow. UK.
REVIEW RETURNED	27-Apr-2015

GENERAL COMMENTS	This paper has improved significantly since the previous version and it is obvious the authors have put a lot of work into it.

	The addition of the COX models is very welcome however their placement at the end of the paper means they get lost when they contain the most valuable information. Plotting the HRs would be a good visual of the results and add greatly to the readers understanding. My suggestion is to plot the HRs for developing hypertension by BMI category for those with an without T2DM on one plot, using normal weight non diabetes as reference category adjusting for age and sex. A similar plot could be used to show sex differences. This should be moved to higher up the paper as the main findings and the text on the regression models shortened considerably. Another suggestion is to move the section justifying the choice of BMI at diagnosis of hypertension from results to methods. I presume table 3 refers to years? This should be clearer.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer's comments

1. "The addition of the COX models is very welcome however their placement at the end of the paper means they get lost when they contain the most valuable information. Plotting the HRs would be a good visual of the results and add greatly to the readers understanding. My suggestion is to plot the HRs for developing hypertension by BMI category for those with and without T2DM on one plot, using normal weight non diabetes as reference category adjusting for age and sex. A similar plot could be used to show sex differences".

We thank the referee for suggestions on replacing the table with a visual plot. The suggestion on doing the Cox analysis on both the data sets of diabetic and non-diabetic individuals with adjusting for both sex and age is a good one and we redid the analysis. Differences in Hazard ratios for diabetic versus non-diabetic individuals emerge clearly and the same clarity is seen with sex-differences.

We now present the results as 'Forest plots' for Hazard Ratios (see the new Figure 2, and page 28 for legends to the new figure). Numerical values are now presented as two supplementary tables. See page 32 for legends to these two supplementary tables.

"This should be moved to higher up the paper as the main findings".

We have carried out this suggestion – we now present text on Cox analysis right after the text on descriptive statistics of the data set. Please see pages 12 and 13.

Moving up this finding is done everywhere else as well – title (see page 1), abstract (see page 2), author summary(see page 4), methods (see page 10), discussion(see page19), conclusion(see page 21).

2. "and the text on the regression models shortened considerably".

We carried out this suggestion.

(a) The section on confounding in the results section is moved to online supplementary information and summarized in the main manuscript (see pages 15 and 30).
(b) The section on regression analysis using the third data set (those who are destined to become diabetic) is shortened (see pages 15 and 16).
(c) Shortening of texts was also carried out (see page 15).

3. “Another suggestion is to move the section justifying the choice of BMI at diagnosis of hypertension from results to methods”.

We carried out this suggestion. Please see page 9.

4. I presume table 3 refers to years? This should be clearer.

Yes, it refers to years. We have now made this clear by explicitly stating ‘years’ in both the tables of 3 and 4. Please see pages 35 and 36.