

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Incidence and risk factors of type 2 diabetes mellitus in an overweight and obese population: a long-term retrospective study from a Gulf State
<b>AUTHORS</b>	Regmi, Dybesh; Al-Shamsi, Saif; Govender, Romona; Al-Kaabi, Juma

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Hiroshi Yokomichi University of Yamanashi, Japan
<b>REVIEW RETURNED</b>	25-Nov-2019

<b>GENERAL COMMENTS</b>	<p>Doctor Regmi D et al. wrote a manuscript about incidence and risk factors of type 2 diabetes in overweight or obese people in the United Arab Emirates. I would like to present comments to contribute to the manuscript.</p> <p>[Major]</p> <ol style="list-style-type: none"><li>1. Number of participants: The sample size may be relatively small. Could the authors increase the sample size?</li><li>2. Article summary: This part need to be understood shortly. Could the authors condense the contents, please?</li><li>3. Introduction: As a reader, I would like to know in this section why the research need to be conducted in UAE with more rationale and how the prevalence of type 2 diabetes, its complications and its mortality are in UAE.</li><li>4. Additionally, I would like to know why the incidence has been problematic recently.</li><li>5. Table 2 may lack new finding(s) for scientific paper. What are the useful information in this tables?</li><li>6. Table 2: If the authors could not prepare enough sample size, they could analyse the mixed data of both sexes with explanatory variable of sex, in place of analysis with strata of sex.</li><li>7. Category of age group in table 2: It would be apparent that old age would affect diabetes incidence. The research could add the analysis of aged people.</li><li>8. Discussion: Again, I wonder what is new message to readers. This section is written in neat manner of epidemiologic manuscript. However, I think that the authors could add more impact for the results with discussing the problem of the problematic status of the incidence and prevalence of diabetes in the Middle East. Additionally, what evidence could the research add to the current problematic status? Further, what could the clinicians and non-diabetics in UAE do for prevention of diabetes and decrease mortality from diabetes?</li></ol>
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	<p>9. The number of tables is relatively small. I consider that the authors could add tables and figures of prevalence and crude incidence of the participants and current national trend of UAE.</p> <p>[Minor]</p> <p>10. Methods: Definition of overweight and obese need to be cited from references.</p> <p>11. Cutoff point of HbA1c of table 2: How did the authors determine the cutoff point of HbA1c for 5.7%?</p> <p>I consider that this manuscript may contribute to the field of diabetes epidemiology, with appropriate modification and add-on of tables and figures.</p>
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<b>REVIEWER</b>	Beatriz D. Schaan
<b>REVIEW RETURNED</b>	Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil 12-Feb-2020

<b>GENERAL COMMENTS</b>	<p>The study is described aimed to evaluate the incidence and risk of developing type-2 DM among individuals with above-normal BMI from a tertiary care center in the UAE. The background is interesting, but some aspects deserve attention, as follows:</p> <ol style="list-style-type: none"> <li>1. Information regarding diabetes prevalence in UAE is not correct (line 73, reference 2)</li> <li>2. Reference 5, line 77, refers to men only. Please change for a correct reference.</li> <li>3. It is not clear why the incidence of T2DM should be searched for in a small center from a tertiary care center. This certainly introduces a selection bias. Moreover, the authors claim that these patients are healthy; why healthy patients are being seen in a hospital? The clinical question here presented should be answered with a population-based research. This is a very significant limitation of this study.</li> <li>4. How did the authors come to the number of 432 patients at baseline? How many records were searched for? More details should be provided here.</li> <li>5. Did the authors calculated the sample size?</li> <li>6. What method was used for HbA1c evaluation? The test results should be standardized to the International Federation of Clinical Chemistry (IFCC) Reference Measurement Procedure (RMP) in harmony with the efforts of the National Glycohemoglobin Standardization Program (NGSP).</li> <li>7. HbA1c can be used for diabetes diagnosis if it is repeated twice;</li> <li>8. Results: There is no need for 2 decimals in the majority of the variables described in tables; The low number of cases precludes analyses by groups (men and women); please, present data from the whole sample.</li> <li>9. The discussion should be written again with less enthusiasm, considering the possible biases suggested above.</li> </ol> <p>There is no possible comparison between these data and reference 8, since reference 8 refers to a population-based study. A possible explanation for not observing an association between HbA1c &gt;5.7% and T2DM incidence can be the sample size.</p>
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## VERSION 1 – AUTHOR RESPONSE

REVIEWER #1 Hiroshi Yokomichi, University of Yamanashi, Japan:

Thank you for your valuable comments on our manuscript. The following are our point-by-point responses.

Doctor Regmi D et al. wrote a manuscript about incidence and risk factors of type 2 diabetes in overweight or obese people in the United Arab Emirates. I would like to present comments to contribute to the manuscript.

[Major]

1. Number of participants: The sample size may be relatively small. Could the authors increase the sample size?

Author's response: Thank you for your comment. The sample size was calculated based on the anticipated incidence of diabetes of 17.3% (based on the International Diabetes Federation data on the United Arab Emirates) and using 80% power at a 2-sided level of significance of 0.05. The result was 353. The sample size was further increased by 20% to account for patients lost to follow-up and those with missing data.

The following paragraph has been added to the Statistical analyses section for clarification, page 7, lines 146–149:

“Using a formula by Rosner (2015),[21] a sample size of 353 was calculated. This was based on the anticipated incidence of diabetes of 17.3% [22] and using 80% power at a two-sided significance level of 0.05. The sample size was further increased by 20% to account for patients lost to follow-up and those with missing data.”

2. Article summary: This part need to be understood shortly. Could the authors condense the contents, please?

Author's response: Thank you for your comment. We have made the appropriate edits and condensed the material in the Article Summary as suggested.

It now reads as follows on Page 3:

- This long-term longitudinal cohort study determines the incidence rate and risk factors of type 2 diabetes mellitus in overweight and obese United Arab Emirates nationals.
- Anthropometric and laboratory data were obtained instead of self-reported information for the classification of risk factors and identification of incident cases.
- The study's subjects were recruited from a single large public hospital's ambulatory clinics; therefore, our findings may not apply to the general UAE population.
- No data were available for review regarding additional confounders, such as family history and changes in weight and physical activity.”

3. Introduction: As a reader, I would like to know in this section why the research need to be conducted in UAE with more rationale and how the prevalence of type 2 diabetes, its complications and its mortality are in UAE.

Author's response: Thank you for your comment. The prevalence of overweight, obesity, and diabetes are much higher in the UAE in comparison to countries like in Western Europe and North America. Furthermore, the prevalence of complications of obesity and diabetes is also higher in the UAE leading to one of the highest mortality rates from cardiovascular disease. Considering that very few

long-term longitudinal studies are available related to this subject matter in the region, we feel that these findings present a strong rationale for the research to be conducted in the UAE.

As such the following paragraphs have been added to the Introduction section, page 3, lines 63–67: “In a 2007 study, the age-standardized rates for prediabetes and type 2 DM among UAE nationals were 24.2% and 29%, respectively.[1] However, in a 2019 study of young Emirati men, the age-adjusted prevalence of prediabetes was much higher at 41.3%.[2] By contrast, the prevalence of type 2 DM in North America and Western European countries are well below 12%.[3-6]”

Page 4, lines 70–80:

“More recently, the age-adjusted prevalence of overweight and obesity among Emirati men between the ages of 18 and 30 years was noted to be 27% and 30%, respectively.[2] In contrast, the corresponding prevalence in another study was 23% and 10% among young Emirati women.[10] Both these studies determined increased BMI to be strongly associated with diabetes.

Both obesity and type 2 DM are well known cardiometabolic risk factors for vascular complications, such as coronary heart disease and peripheral vascular disease. The prevalence of these vascular diseases in the UAE is 10.5% and 11.1%, respectively.[1] These and other vascular-related complications have resulted in the UAE having one of the highest reported global death rates for cardiovascular disease—204 per 100,000 for women and 309 per 100,000 for men.[11]”

4. Additionally, I would like to know why the incidence has been problematic recently.

Author’s response: Thank you for your comment. The reason for the lack of incidence studies on type 2 DM in the UAE is due to time and resource constraints. Incidence studies typically require a long-term follow-up of a defined population cohort and intensive monitoring of laboratory and anthropometric measurements of individuals in the population which can require significant resource investment.

The following sentences have been added to the Introduction section, pages 4–5, lines 81–93:

“The rise in the incidence of diabetes and its complications among the UAE population has been in parallel to the economic surge, resulting in growing urbanization and changing lifestyle habits in the country. Nevertheless, over the last decade, UAE has diverted its attention and endeavored to curb the burden of overweight and obesity, as well as to decrease the incidence of associated conditions like diabetes. The Weqaya program, a population-wide CVD screening program, was initiated in 2008[12] to enable individuals and healthcare providers to implement CVD preventative measures. For continued assessment of the effectiveness of these local interventions, ad hoc analysis of population data at pre-defined intervals over a long period is required. However, epidemiological studies on type 2 DM in the UAE have primarily focused on its prevalence in the general population.[1, 2, 13] Despite having information from the Weqaya program, data regarding the incidence of type 2 DM among obese and overweight UAE nationals remains poorly researched. This lapse is primarily because of the significant resource investment required to conduct observational cohort studies with prolonged follow-up.”

5. Table 2 may lack new finding(s) for scientific paper. What are the useful information in this tables?

Author’s response: Thank you for your comment. The aim of Table 2 was to examine and describe the relationship between the set of predictor variables and type 2 diabetes in our sample population, stratified by sex. Providing a sex-informed perspective increases rigor, promotes discovery and expands the relevance of biomedical research particularly when there is a paucity of sex differences long-term research on diabetes in the United Arab Emirates. Furthermore, while some of the results in this table are not novel, what we found interesting was when adjusted for all other variables, age  $\geq$  44 years in women was found to be a significant risk factor for the development of type 2 diabetes. A

plausible explanation for this finding has been described in the discussion section of the manuscript (page 12, lines 233–238).

6. Table 2: If the authors could not prepare enough sample size, they could analyse the mixed data of both sexes with explanatory variable of sex, in place of analysis with strata of sex.

Author's response: Thank you for your comment. We do understand that analyzing the entire cohort would increase the power of the study, however, as mentioned above (comment # 5), we feel that providing a sex-informed perspective is important particularly when there are very few sex differences longitudinal studies available on diabetes in the United Arab Emirates. We have however reanalyzed the mixed data of both sexes with the explanatory variable of sex as suggested and included the results in Table 2.

7. Category of age group in table 2: It would be apparent that old age would affect diabetes incidence. The research could add the analysis of aged people.

Author's response: Thank you for your comment. We do agree that old age would affect the incidence of diabetes. However, when we split the age variable into 3 categories, there were only 40 patients aged over 64 years during re-analysis. On further examination, there was a lack of association between age  $\geq$  64 years and incident diabetes in the multivariable cox regression analysis. This might be related to a lack of power, considering the wide confidence interval we found on re-analysis. We, therefore, decided to keep the age category as 2 groups for the multivariable cox regression analysis but graphically represented the incident rate of type 2 diabetes with increasing patient age in a new figure (figure 2).

8. Discussion: Again, I wonder what is new message to readers. This section is written in neat manner of epidemiologic manuscript. However, I think that the authors could add more impact for the results with discussing the problem of the problematic status of the incidence and prevalence of diabetes in the Middle East. Additionally, what evidence could the research add to the current problematic status? Further, what could the clinicians and non-diabetics in UAE do for prevention of diabetes and decrease mortality from diabetes?

Author's response: Thank you for the comment and valuable suggestions. We embarked on this project to obtain an accurate incidence of type 2 diabetes in the overweight and obese UAE national population. This is the first long-term study, both in the UAE and in the region that has evaluated the incidence in this high-risk population. The only incidence study to date has been a retrospective cohort study by Sreedharan et al. (2015) which found the incidence rate in the general UAE population to be 4.8/1000 person-years, however, the follow-up period was only one year. Both ours and the 2015 study provide vital baseline data regarding incidence rates in the UAE. As such, target intervention programs are needed to address the high incidence rates of diabetes by reducing its associated risks such as overweight and obesity.

The following paragraph has been edited and expanded in the discussion section in page 13–14, lines 252–265:

“In the UAE, much of the increase in type 2 DM has occurred because of social and economic changes—from traditional, semi-nomadic lifestyle to sedentary, urban, and high-income lifestyle. Consequently, the progression toward type 2 DM and cardiovascular disease starts early in the UAE because of the high prevalence of childhood obesity.[1, 34] A 2015 study of Emirati children and adolescents with a BMI  $\geq$ 25 kg/m<sup>2</sup> determined the prevalence of prediabetes and type 2 DM to be

5.4% and 0.87%, respectively.[35] Therefore, reducing the burden of type 2 DM in the UAE will require intensive population-wide interventions to promote regular physical activity and a healthy diet,[33, 36] particularly among the Emirati youth.

Furthermore, the results of this study highlight the need to focus on Emirati women as a specific target group for obesity prevention programs. These programs should begin in childhood because 21% are obese by the time they are 30 years of age.[26] In addition, it is imperative to have a multidisciplinary approach to address the high incidence of type 2 DM, wherein pediatricians, primary care providers, dietitians, and specialists work collaboratively toward promoting weight reduction and maintaining a healthy BMI in our population.”

9. The number of tables is relatively small. I consider that the authors could add tables and figures of prevalence and crude incidence of the participants and current national trend of UAE.

Author’s response: Thank you for the suggestion. We have added an additional figure that graphically represents the incident rate of type 2 diabetes with increasing patient age (figure 2).

[Minor]

10. Methods: Definition of overweight and obese need to be cited from references.

Author’s response: Thank you for your comment. The World Health Organization (WHO) definition of overweight and obesity on page 4, line 70 and page 6, line 124 are cited (reference #8), and in addition, the WHO online link has been updated in the references.

11. Cutoff point of HbA1c of table 2: How did the authors determine the cutoff point of HbA1c for 5.7%?

Author’s response: Thank you for your comment. The cut-off point of 5.7% for HbA1c is based on the American Diabetes Association criteria used to define prediabetes. To clarify, the following lines have been added, in the Methods, Definitions and measurements section, page 6, line 128:  
“Prediabetes was defined as having an HbA1c level between 5.7% and 6.4%.[19]”

I consider that this manuscript may contribute to the field of diabetes epidemiology, with appropriate modification and add-on of tables and figures.

Author’s response: Thank you for your valuable comments. We have made the appropriate modifications to the manuscript and provided an additional figure as suggested.

REVIEWER #2 Beatriz D. Schaan, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil:  
Thank you for your valuable comments on our manuscript. The following are our point-by-point responses.

The study is described aimed to evaluate the incidence and risk of developing type-2 DM among individuals with above-normal BMI from a tertiary care center in the UAE. The background is interesting, but some aspects deserve attention, as follows:

1. Information regarding diabetes prevalence in UAE is not correct (line 73, reference 2)

Author’s response: Thank you for pointing this out. According to the reference (Saadi H et al.), the age-standardized rates for diabetes both diagnosed and undiagnosed was 29.0%. For clarification, page 3, line 63 has been modified:

“In a 2007 study, the age-standardized rates for prediabetes and type 2 DM among UAE nationals were 24.2% and 29%, respectively.[1]”

2. Reference 5, line 77, refers to men only. Please change for a correct reference.

Author's response: Thank you for pointing this error out. Reference # 5 has been replaced with an updated reference:

Ganz ML, Wintfeld N, Li Q, et al. The association of body mass index with the risk of type 2 diabetes: a case–control study nested in an electronic health records system in the United States. *Diabetology & Metabolic Syndrome* 2014;6:50. doi:10.1186/1758-5996-6-50

3. It is not clear why the incidence of T2DM should be searched for in a small center from a tertiary care center. This certainly introduces a selection bias. Moreover, the authors claim that these patients are healthy; why healthy patients are being seen in a hospital? The clinical question here presented should be answered with a population-based research. This is a very significant limitation of this study.

Author's response:

Thank you for your comments. While we understand the reviewer's concern, however, we would like to clarify that there are approximately 100,000 adult UAE citizens in Al-Ain, and approximately 60% are overweight or obese. Therefore, our study cohort represents an estimated 1% of overweight or obese UAE adults in Al-Ain. Furthermore, Tawam Hospital is one of two large publicly funded facilities, and its outpatient medical clinics serve most of the UAE nationals of Al-Ain.

We feel that the results of our study are relevant, because a cohort study of relatively long duration, such as ours, in the Middle Eastern region where available data on the subject matter is sparse, in our opinion, fills a gap in the literature. In addition, our results will be available to compare with future studies in the UAE and with neighboring countries.

The following section has been edited for better clarification, Methods section, page 5, line 102:

“Tawam Hospital is one of the two large government hospitals in the city of Al Ain and serves an estimated 60,000 adult UAE nationals in the city who are overweight and obese.[14, 15]”

We have also added the following lines in the limitation section, highlighting the important point raised by the reviewer.

Discussion, Strengths and limitations section Page 14, line 278:

“Finally, subjects for this study were recruited from a single largest tertiary care hospital's ambulatory clinics; thus, our findings may not apply to the general UAE population.”

Regarding the term 'healthy' used to describe the study cohort. The term was used to imply that the patients did not have a history of chronic medical conditions such as malignancy, human immunodeficiency virus infection, or stage 3–5 chronic kidney disease. However, we agree the term may be confusing therefore the word 'healthy' has been removed.

4. How did the authors come to the number of 432 patients at baseline? How many records were searched for? More details should be provided here.

Author's response: Thank you for your comment. The sample size was calculated based on the anticipated incidence of diabetes of 17.3% (based on the International Diabetes Federation data on the United Arab Emirates) and using 80% power at a 2-sided level of significance of 0.05. The result was 353. The sample size was further increased by 20% (approximately 430 patients) to account for patients lost to follow-up and those with missing data.

The following paragraph has been added to the Statistical analyses section for clarification, page 7, lines 146–149:

“Using a formula by Rosner (2015),[21] a sample size of 353 was calculated. This was based on the anticipated incidence of diabetes of 17.3% [22] and using 80% power at a two-sided significance level

of 0.05. The sample size was further increased by 20% to account for patients lost to follow-up and those with missing data.”

5. Did the authors calculated the sample size?

Author’s response: Thank you for your comment. Yes, the sample size was calculated.

The following paragraph has been added to the Statistical analyses section for clarification, page 7, lines 146–149:

“Using a formula by Rosner (2015),[21] a sample size of 353 was calculated. This was based on the anticipated incidence of diabetes of 17.3% [22] and using 80% power at a two-sided significance level of 0.05. The sample size was further increased by 20% to account for patients lost to follow-up and those with missing data.”

6. What method was used for HbA1c evaluation? The test results should be standardized to the International Federation of Clinical Chemistry (IFCC) Reference Measurement Procedure (RMP) in harmony with the efforts of the National Glycohemoglobin Standardization Program (NGSP).

Author’s response: Thank you for your comment. HbA1c levels were measured using an automated analyzer Integra 400 Plus (Roche Diagnostics, Mannheim, Germany) (Page 7, line 140). The HbA1c results are reported as a percentage using the IFCC-NGSP master equation.

For clarification, the following line has been added, page 7, line 141:

“The HbA1c results were reported as a percentage using the International Federation of Clinical Chemistry-National Glycohemoglobin Standardization Program master equation.[20]”

7. HbA1c can be used for diabetes diagnosis if it is repeated twice;

Author’s response: Thank you for your comment. In this study, the outcome was incident type 2 diabetes which was defined as at least two documented HbA1c levels of  $\geq 6.5\%$ . This definition was based on the American Diabetes Association’s diagnosis and classification of diabetes mellitus.

For clarification, the following line has been added, page 6 line 135:

“... (based on the definition of DM by the American Diabetes Association)”

8. Results: There is no need for 2 decimals in the majority of the vriables described in tables; The low number of cases precludes analyses by groups (men and women); please, present data from the whole sample.

Author’s response: Thank you for your comment. We do understand that analyzing the entire cohort as one would increase the power of the study, however, we feel that providing a sex-informed perspective increases rigor, promotes discovery, and expands the relevance of biomedical research particularly when there is a paucity of sex differences long-term research in diabetes in the United Arab Emirates. We have however reanalyzed the data from the whole sample as suggested and included the results in Table 2. We have also reduced the number of decimal points in Table 1 as suggested.

9. The discussion should be written again with less enthusiasm, considering the possible biases suggested above.

Author’s response: Thank you for your comment. The discussion section has been edited while taking the limitations of the study in mind.



10. There is no possible comparison between these data and reference 8, since reference 8 refers to a population-based study.

Author's response: Thank you for your comment, We agree that comparing our study results with the only other incidence study from the UAE by Sreedharan et al. (2015) is not possible because that study was conducted on the general population rather than overweight or obese UAE nationals, such as ours.

For clarification, the following line has been added to page 12 line 230:

"However, this study cannot be directly compared with our study because it was conducted on the general population, and our study cohort comprised only overweight and obese UAE nationals."

11. A possible explanation for not observing an association between HbA1c >5.7% and T2DM incidence can be the sample size.

Author's response: Thank you for your comment. We agree, the sample size of our study could explain the lack of association seen between HbA1c  $\geq$ 5.7% and incident diabetes in women, therefore as suggested by your comment #8, we re-analyzed the entire cohort and included the results in Table 2. On the re-analysis of the entire cohort, we observed a significant association between HbA1c  $\geq$ 5.7% and incident diabetes.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Hiroshi Yokomichi University of Yamanashi, Japan
<b>REVIEW RETURNED</b>	16-Mar-2020
<b>GENERAL COMMENTS</b>	The researchers have addressed all of my comments. I have no more concern. I appreciate their efforts to report the important results.