

Dear Editor,

Please find enclosed the edited manuscript in Word format

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 20209

Tipping the balance – Haemoglobinopathies and the risk of diabetes.

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The manuscript has been improved according to the suggestions of reviewers 1 Format has been updated and revised according to the editors embedded comments.

2 comments from reviewers (responses in bold)

Dear editor,

Many thanks for your comments. Here follow the revisions, as per your suggestions:

- *"A paediatric study of 860 individuals in Western Kenya reported 38.5% were heterozygous and 9.5% for α -thalassaemia"* has been amended to now read, *"A paediatric study of 860 individuals in Western Kenya reported 38.5% were heterozygous and 9.5% were homozygous for α -thalassaemia"*.
- *"Çukrova" in Turkey, which should be "Çukurova"* has now been amended accordingly.
- *"an hepatocyte model"* now reads, *"a hepatocyte model"*.
- In response to the comment, *"The prevalence figures in the paragraphs just before the Conclusion section will be more useful with more evaluative sentences as to whether an association may be present [...]"*, the paragraph has been revised to now read,

"The prevalence of diabetes in sub-Saharan Africa is reported as being between 1% (rural Uganda) and 12% (Nairobi)^[46]. A paediatric study of 860 individuals in Western Kenya reported 38.5% were heterozygous and 9.5% homozygous for α -thalassaemia. Sickle-cell trait was present in 17.2% and Sickle-cell disease in 1.8%^[47]. This demonstrates a relatively high prevalence of both diabetes and haemoglobinopa-

thies, calling for the need for further investigation to directly compare diabetes and haemoglobinopathies in each of these populations. Prevalence of diabetes in India is 9.1%, with the cumulative gene frequency of haemoglobinopathies being 4.2%, with large variation between different ethnic groups^[48]. Again, direct study of both conditions in these individual ethnic groups is needed in order to draw more meaningful comparison. Turkey is of particular interest as the prevalence of diabetes is 14.8%, but Sickle-cell disease is only found in 0.3%, which suggests a lesser correlation than in India and Africa. There are areas of Turkey, however, (i.e. Çukurova) where the prevalence of carriers of HbAS is as high as 44%^[49,50]. A similar affect has been reported in Madang in Papa New Guinea, where 97% of the population tested were either heterozygous or homozygous for α -thalassaemia^[51]. The overall prevalence of diabetes in Papa New Guinea is 5.2%^[52], however it would be interesting to examine the populations of Madang and Çukurova for diabetes prevalence specifically due to the extremely high rates of α -thalassaemia and HbAS. The U.S.A. provides interesting data. The overall prevalence of diabetes is 9.2%, with 13.2% of African Americans affected^[53]. The highest rates of diabetes in the U.S. are actually amongst American Indians and Alaskan natives (15.9%)^[53], where the prevalence of Sickle-cell disease is 36.2/100000 live births, making these ethnic groups the third most affected by Sickle-cell disease behind African Americans (289/100000) and Hispanics (89.1/100000)^[54,55]. Hb-E occurs widely throughout the eastern half of the Indian subcontinent, Bangladesh, Myanmar, and East and Southeast Asia. Most notably in the Northern parts of Thailand and Cambodia, where the region is referred to as the 'Hb-E Triangle' where up to 70% are carriers^[44,45]. The prevalence of diabetes in these areas is 8.5% (Thailand)^[56] and 2.6% (Cambodia)^[57].

Although, on the whole, it is difficult to determine any firm correlations using the above sources, the existing data certainly summons enough intrigue to warrant further investigation."

We would like to thank the Editor and the reviewers for their time and support with this manuscript and we hope that the manuscript is sufficiently improved for publication.

Yours Sincerely

 5/10/15

Jeetesh V Patel.