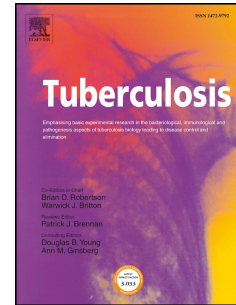# Accepted Manuscript

Diabetes screen during tuberculosis contact investigations highlights opportunity for new diabetes diagnosis and reveals metabolic differences between ethnic groups

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1 **Diabetes screen during tuberculosis contact investigations highlights opportunity for new diabetes**

2 **diagnosis and reveals metabolic differences between ethnic groups**

3

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44 **List of abbreviations**

45 T2D: Type 2 diabetes; TB: Tuberculosis; WHO: World Health Organization; BMI: body-mass index; LDL-c:

46 Low-density lipoprotein cholesterol; HDL-c: High-density lipoprotein cholesterol; HIV: Human

47 immunodeficiency virus; HOMA-IR: homeostasis model assessment for insulin resistance; LTBI: Latent TB

48 infection; PCA: Principal Component Analysis; ANCOVA: Analysis of covariance

49

50

51 **Abstract**

52 Type 2 diabetes (T2D) is a prevalent risk factor for tuberculosis (TB), but most studies on TB-T2D have

53 focused on TB patients, been limited to one community, and shown a variable impact of T2D on TB risk

54 or treatment outcomes. We conducted a cross-sectional assessment of sociodemographic and metabolic

55 factors in adult TB contacts with T2D (versus no T2D), from the Texas-Mexico border to study Hispanics,

56 and in Cape Town to study South African Coloured ethnicities. The prevalence of T2D was 30.2% in

57 Texas-Mexico and 17.4% in South Africa, with new diagnosis in 34.4% and 43.9%, respectively. Contacts

58 with T2D differed between ethnicities, with higher smoking, hormonal contraceptive use and cholesterol

59 levels in South Africa, and higher obesity in Texas-Mexico (p <0.05). PCA analysis revealed striking

60 differences between ethnicities in the relationships between factors defining T2D and dyslipidemias.

61 Our findings suggest that screening for new T2D in adult TB contacts is effective to identify new T2D

62 patients at risk for TB. Furthermore, studies aimed at predicting individual TB risk in T2D patients, should

63 take into account the heterogeneity in dyslipidemias that are likely to modify the estimates of TB risk or

64 adverse treatment outcomes that are generally attributed to T2D alone.

65

67

68

69 **1.   Introduction**

70 The growing pandemic of type 2 diabetes mellitus (T2D) is a challenge to tuberculosis (TB) control.

71 Individuals with T2D have a 3-fold increased risk of TB, particularly if they have poor glucose control or

72 additional T2D complications [1-3]. However, the increased TB risk in patients with T2D varies widely

73 between studies, regions and populations, with risk estimates ranging from 0.99 to 7.83. Likewise, at the

74 population level, the contribution of T2D to TB is generally between 10-20%, with substantial variation

75 depending on the local epidemiology [1, 4].

76

77 Once a patient with T2D develops TB, they appear to be more likely to have delays in the conversion of

78 sputum smears from positive to negative during TB treatment, to fail treatment, or to relapse [5-7].

79 However, not all studies report these associations between adverse treatment outcomes and T2D, and if

80 so, there are variations in their magnitude. This heterogeneity illustrates the complexity of studying T2D

81 as a risk factor for TB and may be explained by variability in study populations with respect to T2D (e.g.,

82 glucose control, medications, co-morbidities), sociodemographics and access to healthcare, or variations

83 in study designs [8]. Few interactions between T2D and other host characteristics have been described,

84 as suggested for T2D plus smoking or micro and macro-vascular diseases [9-12]. While more studies of

85 this nature are needed among TB patients, there are even fewer studies in TB contacts with T2D. This is

86 a particularly important population for TB control given that TB contacts have one of the highest risks

87 for TB progression (5% in the first year of exposure to a pulmonary TB patient), and those with T2D will

88 magnify this risk by 3-fold [3, 13].

89

90 The goal of the present study was to compare sociodemographic and metabolic risk factors for TB

91 among TB contacts with T2D from two distant communities with differing ethnicities and cultures. We

92 enrolled South African Coloureds in the Western Cape of South Africa (TB 625/100,000/year; HIV <6%;

93 T2D range 8-28%), and Hispanics in south Texas (T2D 19%; HIV 0.14/100,000; TB 10/100,000/year) and

94 northern Mexico (T2D 15%; TB 32/100,000/year) [1, 14-16]. Our study revealed two major findings: A

95 high frequency of new T2D among the TB contacts from both regions, and striking differences between

96 ethnicities in metabolic and sociodemographic characteristics that are likely to modify the risk of TB

97 conferred by T2D.

98

99 **2.   Methods**

4

100 Participants were enrolled at clinics in south Texas (Hidalgo and Cameron County Health Departments),

101 northern Mexico (Centro Regional de Tuberculosis in Reynosa; 'Texas-Mexico' in this study) and South

102 Africa (public healthcare clinics around the Tygerberg Academic Hospital in Cape Town; 'South Africa' in

103 this study). Close contacts were defined as sharing at least 5 hours per week in a house or closed space

104 with a confirmed pulmonary TB source. Active TB was ruled out based on lack of signs and symptoms

105 compatible with TB, and by normal chest x-ray (routine in Texas and South Africa, and upon physician

106 request in Mexico). At both study sites, we enriched for T2D by initially enrolling contacts 30-65 years

107 old and eventually elevating the lower age to 35 years. In South Africa, all eligible participants were

108 screened for T2D by HbA1c and FBG to determine accurate prevalence data. From those, all participants

109 with an HbA1c ≥ 6.5 % were fully enrolled into the study and blood samples were collected for the

110 downstream analysis, whereas only randomly selected participants with HbA1c ≤ 6.5% were enrolled on

111 the basis of one normoglycemic participant per participant with hyperglycemia. Exclusion criteria

112 included a body-mass index (BMI) < 18.5, HIV infection, type 1 diabetes, cancer and recent infections.

113 The study was approved by the institutional review boards of the participating institutions and

114 participants signed a free informed consent.

115

116 Diabetes classification was based on hyperglycemia (fasting plasma glucose ≥126 mg/dL), HbA1c ≥ 6.5%

117 or self-report, and pre-T2D as HbA1c 5.7-6.49% [17]. Macro- and micro-vascular pathologies were self-

118 reported. The frequency of alcohol consumption and the average number of alcoholic drinks consumed

119 in a typical day were established using validated questions described previously [18]. Alcohol excess was

120 defined as drinking ≥7 drinks/episode at least weekly or binge drinking (≥10 drinks/episode at least

121 twice a month), and alcohol abuse was defined as consumption of more than 7 drinks per day on a daily

122 basis. Drug use was based on self-reported use of injectable or non-injectable illicit drugs at least twice

123 per week. Latent TB infection (LTBI) was based on QuantiFERON-Gold In-Tube (Qiagen). Plasma LDL

124 cholesterol (LDL-c) was measured in South Africa, and calculated for Texas [Total cholesterol - HDL-c -

125 (Triglycerides *0.20)] [19]. Insulin resistance was based on the homeostasis model assessment (HOMA-

126 IR) [fasting plasma glucose (mM)*fasting serum insulin (mU/L)/22.5] on participants who did not use

127 insulin [20].

128

129 Data were entered into RedCap (Vanderbilt University) and exported into SAS (v9.4 Cary, NC) or SPSS

130 (v23.0 Armonk, NY) for analysis. Chi-square or Fisher's exact tests were used to compare categorical

131 variables and two-sample test proportions to identify differences between study sites. Mixed-model

132 designs for analysis of covariance (ANCOVA) were performed and the F statistic transformed to Cohen-d.

133 A Latent Factor analysis using Principal Components approach (PCA) was done and Varimax axes

134 rotation was used for eigen vector interpretation. P values were considered significant if ≤ 0.05, and

135 marginally significant if <0.1.

136

137 **3.   Results**

138 3.1   Characteristics of all TB contacts

139 We enrolled 95 contacts (after screening 247 for T2D) in South Africa, and 106 in Texas-Mexico (46 in

140 Mexico and 60 in Texas; all those screened were enrolled). The contacts from both sites were

141 predominantly females, but differed in several aspects: In Texas-Mexico nearly all (98%) were Hispanic

142 whites and in South Africa all were South African Coloureds, a mixed ancestry population with Khoisan,

143 Bantu, European and Asian roots. The Texas-Mexico contacts were younger, more educated and obese

144 (Table 1 and Fig 1A; $p<0.001$), while those in South Africa were more likely to smoke and there was a

145 higher proportion of females reporting contraceptive use ($p<0.003$). Their medical history differed

146 between study sites in various ways (Table S1). Those in Texas-Mexico were more likely to have a family

147 history of T2D ($p=0.005$), take anti-inflammatory medications ($p=0.002$) or vitamin supplements

148 ($p=0.001$) and were less likely to have previous TB or current LTBI ($p <0.001$).

149

150 3.2   Prevalence of pre-T2D and T2D

151 In Texas-Mexico we identified 32 contacts with T2D (30.2%) and 26 with pre-T2D (24.5%; 54.7% with

152 both). In South Africa, we screened for elevated HbA1c in 247 TB contacts and identified 43 with T2D

153 (17.4%) and 56 with pre-T2D (22.7%; 40.1% with both). Thus, the prevalence of T2D and pre-T2D was

154 high in both communities, and significantly higher in Texas-Mexico ($p=0.007$). Among those with T2D,

155 34.4% were newly diagnosed in Texas-Mexico and 43.9% in South Africa. In South Africa, we invited all

156 of the pre-screened contacts with T2D and a similar number of no T2D controls (without taking into

157 account pre-T2D status) for full enrollment [total n=95; 41 (43.2%) with T2D and 21 (22.1%) with pre-

158 T2D].

159

160 3.3   Sociodemographic and medical history by T2D status and study site

161 Analysis was done by T2D status (2 categories) and also including pre-T2D (3 categories), but the latter

162 results are only described when there were detectable differences in the pre-T2D group. The contacts

163 with T2D (versus no T2D) were older at both study sites, and in South Africa they were also more likely

6

164 to be obese and female (Table 1). Contacts with T2D (versus no T2D) from both study sites were more

165 likely to have a family history of T2D, and a higher frequency of macro or micro-vascular complications.

166 Between study sites, the T2D contacts from Texas-Mexico (versus South Africa) had a higher level of

167 education, were more obese and had higher waist-hip ratios, but reported less smoking (p<0.001) or

168 hormonal contraceptive use (Table 1; p=0.003). The T2D patients from Texas-Mexico (versus South

169 Africa) were more likely to take anti-inflammatory medications (p=0.006) and vitamin supplements

170 (p=0.017), but they were less likely to have a previous history of TB (p=0.013) or current LTBI (p=0.008;

171 Table S1).

172

173 3.4   Glucose metabolism-related characteristics by T2D status and study site

174 There were three differences between the T2D contacts from both study sites with respect to glucose

175 metabolism. First, there was a trend for a higher proportion of elevated HbA1c in the presence of

176 otherwise normal fasting plasma glucose in South Africa (34.1%) versus Texas-Mexico (18.2%); Figure 2;

177 p = 0.128). The second difference was related to insulin resistance. As expected, insulin levels and insulin

178 resistance (HOMA-IR) were higher among the T2D contacts (Table 2), but insulin resistance was also

179 higher in the no T2D contacts from Texas-Mexico versus South Africa (p=0.017). We hypothesize this

180 difference was related to the higher BMI and triglycerides in Texas-Mexico (Tables 1, 2; Figs 1,4), given

181 that insulin resistance is associated with obesity and can be driven by free fatty acids, which are

182 triglyceride metabolites [21]. Thus, we evaluated the relationships between BMI or triglycerides on

183 HOMA-IR. As expected, in each country we found that HOMA-IR values were positively correlated with

184 triglycerides (rho=0.34 in Texas-Mexico; rho=0.37 in South Africa; p <0.001) and BMI (rho=0.38 in Texas-

185 Mexico; rho=0.53 in South Africa; p <0.001; Fig S1). Because these bivariate analyses showed dispersion

186 (an indication of error due to the contribution of other variables to HOMA-IR), we tested several models.

187 Smoking, drugs, alcohol and contraceptives were not associated with HOMA-IR. The model with the best

188 fit for the HOMA-IR variable required adjustment for study site, age and sex, and the interaction

189 between BMI*triglycerides (Cohen d = 0.95, p<0.001, Fig 3A). We further visualized these adjusted

190 relationships with 3D surface plots (Figs 3B-C). At both study sites, the simultaneous increase in BMI and

191 triglycerides was correlated with increased adjusted HOMA-IR, but in South Africa some individuals also

192 had high adjusted HOMA-IR despite normal triglycerides. This ANCOVA model revealed a third

193 difference in glucose metabolism between study sites: a differential contribution of sex to adjusted

194 HOMA-IR by study site, with higher insulin resistance in women from South Africa (mean 5.5, 95% CI 4.7,

195 6.2) versus Texas-Mexico (mean 3.9, 95% CI 3.2, 4.7; Figure S2).

7

196

197   3.5   Lipid metabolism-related characteristics by study site and T2D status

198   The contacts from both study sites differed in their lipid profiles (Table 2). The most prevalent

199   dyslipidemias were high triglycerides and low HDL (among females) in Texas-Mexico and high LDL-c

200   cholesterols in South Africa (p<0.05). The contacts with T2D (versus no T2D) from both study sites were

201   more likely to have high triglycerides and total cholesterol (Table 2). Sex also had an effect on altered

202   HDL-c, with differences between countries. Smoking, drugs, alcohol and contraceptives were not

203   associated with lipids in either country.

204   We expanded on the observed differences by analyzing the influence of study sites, T2D status, sex and

205   age, on the various lipid levels. We found that triglycerides were higher in Texas-Mexico and in T2D

206   patients (Cohen-d= 0.43-0.44; Figure 4A). Total cholesterol was higher in South Africans (Cohen-d= 0.67),

207   but was not affected by T2D status (Figure 4B). HDL-c was lower in pre-T2D and T2D in Texas-Mexico

208   (Cohen-d= 0.43 and 0.5; Figure 4C). Finally, LDLs had an interaction effect between study site and T2D

209   status (Cohen-d= 0.38) (Figure 4D). In summary, lipid levels were mainly influenced by study site and

210   T2D status.

211

212   3.6   Relationship between metabolic factors underlying T2D at both study sites

213   Our analysis of two study populations indicated variable relationships between metabolic factors that

214   define T2D (hyperglycemia, HbA1c, HOMA-IR), obesity (BMI, waist-hip ratio) and dyslipidemias

215   (triglycerides, total cholesterol, LDL-c and HDL-c). To further understand these relationships, we

216   conducted a Latent Factor analysis of these variables using PCA for each study site. We found that South

217   Africa had two components that explained 53% of variability on the seven variables, while Texas-Mexico

218   required four components to describe the relationships between these same variables, and explained

219   79% of total variability (Fig 5; Table S2).

220

221   **4.   Discussion**

222   To our knowledge, this is the first study to provide an in-depth description of the

223   sociodemographic and metabolic characteristics of adult contacts of TB patients from two distant

224   communities with different ethnicities: The Texas-Mexico border region in North America and the

225   Western Cape of South Africa. We report two major findings. First, both communities revealed high

226   prevalence rates (at least 40%) of combined pre-T2D and T2D, and at least 30% of undiagnosed T2D.

227   These statistics provide support for evaluating the expansion of current TB contact screening protocols

228   to include T2D screening. Second, our analysis revealed differences in epidemiologic factors (smoking,

229   education and contraceptive use) and metabolic status (glycated hemoglobin, insulin resistance,

230   dyslipidemia and obesity) between the T2D patients from both ethnicities. Sex had a differential

231   influence by study site on the metabolic status. Definition of these complex relationships is a critical step

232   forward in understanding how these factors affect the magnitude of the contribution of T2D to the risk

233   and adverse outcomes for TB in different ethnic groups.

234   Previous studies have shown that the screening of TB patients for T2D is effective to detect new

235   T2D, particularly in developing countries where T2D awareness is lower [1, 4, 22]. We now find that

236   screening for T2D among adult TB contacts, a population at high risk for TB, can be very effective in

237   identifying individuals with T2D. In Texas-Mexico a lack of T2D awareness was observed on both sides of

238   the border [6/15 (40%) in Texas; 5/17 (29.4%) in Mexico]. Thus, T2D screening among contacts is not

239   only beneficial in developing countries as suggested in a recent report from India, but also in

240   populations with severe health disparities from developed countries.[23] The participating counties in

241   south Texas are among the poorest counties in the US, and the enrolled TB contacts were in the lowest

242   20% percentile of this community (data not shown) [24]. In South Africa, the proportion of new T2D

243   among all T2D patients was even higher at 43.9%, a figure consistent with the estimated lack of T2D

244   awareness in nearly two thirds of the adults with T2D in sub-Saharan Africa [25]. Possible explanations

245   for the high proportion of new T2D among TB contacts is the low access to healthcare in populations at

246   risk for TB, who generally belong to the lower socioeconomic strata [1]. This provides further support for

247   the contribution of TB clinics as hubs for new T2D diagnosis.

248   Our study across two continents also revealed metabolic differences in the TB contacts with

249   T2D. South Africans had a higher proportion of high HbA1c in the presence of normal fasting blood

250   glucose (Fig 2). Our study is not the first to report disparities in HbA1c across ethnicities [15, 26]. It has

251   been hypothesized that higher HbA1c in Africans may result from slower erythrocyte turnover or

252   metabolism [26, 27]. Another possibility is that elevated HbA1c in the South African cohort is due to

253   post-prandial glucose spikes despite normal fasting glucose. This is known to vary between ethnicities

254   [28]. To evaluate an overestimation of T2D among the South African contacts, we estimated the

255   proportion of T2D if we would have used an HbA1C cutoff point of 6.9% as suggested previously [29]

256   (e.g self-report of T2D, glucose ≥ 126 and/or HbA1C ≥ 6.9%). However, we found that the T2D

257   prevalence would be 42.1% with this variation, which is similar to the 43.2% calculated in our study.

258   Insulin resistance was associated with age and sex at both study sites. However, two findings

259   lead us to hypothesize that insulin resistance is largely driven by the higher levels of obesity and

260 triglycerides in Texas-Mexico, and possibly influenced by host genetics in the leaner population from

261 South Africa. First, insulin resistance was associated with high BMI and triglycerides at both study sites,

262 as would be expected for T2D being driven by obesity [30]. However, in South Africa, insulin resistance

263 was also (unexpectedly) higher among individuals with normal triglycerides regardless of BMI,

264 suggesting a genetic component. Second, another unique feature of the South African contacts was the

265 higher insulin resistance among females, regardless of their BMI, triglycerides or age.

266 Lipid profiles also differed by ethnicity with elevated triglycerides more prevalent in Hispanics,

267 and cholesterols in South African Coloureds (Table 2; Fig 4). While higher triglycerides are generally

268 related to obesity, higher cholesterol levels are likely attributed to host genetics [31]. We speculate that

269 high cholesterol may increase TB risk beyond the baseline already conferred by T2D. Support for this is

270 based on reports that host cholesterol favors *M. tuberculosis* survival and growth, increases TB

271 susceptibility in a mouse model, and a lower risk of TB associated with statin therapy (which lowers

272 cholesterol)[32, 33]. The impact of triglycerides on TB risk is unclear, even though *Mtb* has been shown

273 to modulate lipolysis and use fatty acids from the host cell [34].

274 The PCA analysis confirmed that our study sites differ in the relationships between metabolic

275 elements associated with T2D, where some may increase TB risk (total or LDL cholesterol) and others

276 may be protective (e.g. BMI). In South Africa, HOMA-IR and HbA1c were correlated with triglycerides,

277 LDL-c and waist-hip ratio. These are known cardiovascular disease risk factors, particularly for T2D

278 patients [35]. In contrast, in Hispanics, HOMA-IR and HbA1c failed to correlate with these cardiovascular

279 risk factors (Fig 5). These differences in the underlying metabolic status may contribute to the poorly

280 understood variability in TB risk estimates among T2D patients worldwide [4, 11]. For example, recent

281 studies suggest that the higher death rate in TB-T2D patients is due to T2D complications, including a

282 study in Tanzania [9, 11, 36, 37]. Thus, one would predict that TB-T2D patients with cardiovascular

283 diseases are more likely to die. Anecdotally, our studies in Texas-Mexico have failed to detect higher risk

284 of death among TB-T2D patients versus TB alone, even after controlling for potential confounders [38].

285 Sociodemographic factors that increase TB risk were also distributed differently between both

286 study site. Notably, the T2D patients from South Africa had higher smoking rates. Smoking is a risk factor

287 for progression from latent to active TB [39], and the co-existence of T2D plus smoking has been

288 associated with higher risk of TB or higher prevalence of MDR-TB or death during TB treatment [9, 12,

289 40]. A greater proportion of female participants at the South African site reported hormonal

290 contraceptive use. We have shown that medroxyprogesterone acetate decreases *M. bovis* BCG-induced

291 cytokine production in MPA users [41], and increases the *M. tuberculosis* burden in mice [42].

10

292   We recognize study limitations such as a relatively small sample size. Both study sites had a

293   higher proportion of females, which reflect their higher willingness to participate in research studies.

294   Thus, extrapolation of our findings to the entire community must be done with caution.

295   **5.   Conclusions**

296   Our findings have two major implications. First, the high frequency of new T2D patients among

297   adult TB contacts warrants further investigation into the expansion of routine TB contacts investigations

298   to include T2D screening. These are likely to increase significantly the early diagnosis of T2D in

299   economically disadvantaged populations at risk for serious T2D complications and TB development.

300   Second, elucidation of the risk conferred by T2D towards TB development or TB treatment outcomes

301   should be done in the context of other host sociodemographic and metabolic characteristics that may

302   further boost or restrain *M. tuberculosis* survival. We posit that the combination of these variations

303   confers differences in the "hierarchy" of TB risk and treatment outcomes, and future studies aimed at

304   predicting TB risk among the millions of T2D patients worldwide should analyze these host variables.

Ethical approval

Participants signed an informed consent previously approved by the Institutional Review Boards of the University of Texas Health Houston, Secretaria de Salud de Tamaulipas or Stellenbosch University.

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442

Table 1. Sociodemographic characteristics of TB contact, by study site and T2D status[a]

	Texas-Mexico				South Africa				Texas-Mexico vs South Africa[b]		
	All	Type 2 diabetes			All	Type 2 diabetes			All	No T2D	T2D
		No T2D	T2D	P		No T2D	T2D	P	P	P	P
	n=106	74 (69.8%)	32 (30.2%)		n=95	54 (56.8%)	41 (43.2%)				
Age in yrs (median, IQR)	44(13)	42.5(13)	49(16)	**0.011**	49(14)	45.5(13)	53(13)	**<0.001**	**0.030**	0.253	0.208
Age groups				**0.082**				0.107			
30 to 35	17(16%)	15(20.3%)	2(6.3%)		10(10.5%)	8(14.8%)	2(4.9%)		0.253	0.248	0.795
36 to 59	77(72.6%)	53(71.6%)	24(75.0%)		78(82.1%)	44(81.5%)	34(82.9%)		0.110	0.197	0.407
60 to 65	12(11.3%)	6(8.1%)	6(18.8%)		7(7.4%)	2(3.7%)	5(12.2%)		**<0.001**	0.310	0.434
Sex				0.248				**0.021**	0.563	0.791	0.407
Male	35(33%)	27(36.5%)	8(25.0%)		28(29.5%)	21(38.8%)	7(17.1%)				
Female	71(67%)	47(63.5%)	24(75.0%)		67(70.5%)	33(61.2%)	34(82.9%)				
Highest Education				0.830				0.859			
Elementary	12(11.8%)	8(10.8%)	4(14.3%)		10(10.5%)	6(11.1%)	4(9.8%)		0.770	0.957	0.554
Middle	26(25.5%)	18(24.3%)	8(28.6%)		28(29.5%)	14(25.9%)	14(34.1%)		0.526	0.836	0.616
High school	24(23.5%)	19(25.7%)	5(17.9%)		52(54.7%)	31(57.4%)	21(51.1%)		**<0.001**	**<0.001**	**0.004**
College	40(39.2%)	29(39.2%)	11(39.3%)		5(5.3%)	3(5.6%)	2(4.9%)		**<0.001**	**<0.001**	**<0.001**
Smoking				0.606				0.114			
Never smoked	68(64.2%)	46(62.2%)	22(68.8%)		17(20.2%)	11(23.4%)	6(16.2%)		**<0.001**	**<0.001**	**<0.001**
Past smoker	15(14.2%)	10(13.5%)	5(15.6%)		6(7.1%)	1(2.1%)	5(13.5%)		**<0.001**	**0.024**	0.800
Current smoker	23(21.7%)	18(24.3%)	5(15.6%)		61(72.6%)	35(74.5%)	26(70.3%)		**<0.001**	**<0.001**	**<0.001**
Alcohol excess	7(6.6%)	5(6.8%)	2(6.3%)	0.645	4(4.2%)	2(3.7%)	2(4.9%)	0.778	0.476	0.447	0.795
Drugs	5(4.7%)	4(5.4%)	1(3.1%)	0.522	10(10.6%)	8(14.8%)	2(4.9%)	0.134	0.118	**0.071**	0.701
Contraceptive hormones [c]	4(5.6%)	4(8.5%)	0(0%)	0.184	13(19.4%)	9(27.3%)	4(11.8%)	0.109	**0.003**	**0.005**	**0.044**
Waist-Hip ratio [d]				0.153				0.174	**0.001**	**0.006**	**0.018**

Normal	26(26.3%)	21(30.4%)	5(16.7%)		47 (49.5%)	30 (54.5%)	17(42.5%)				
At risk	73(73.7%)	48(69.6%)	25(83.3%)		48 (50.5%)	24 (44.4%)	24 (58.5%)				
BMI (median, IQR)	29.4(7.9)	29.1(8.2)	30.1(7.2)	0.500	26.2(10.5)	24.8(8.6)	28.5(10.8)	**0.008**	**0.002**	**<0.001**	0.421
BMI categories				0.237				**0.064**			
Normal (18.5-24.9)	20(19.0%)	17(23.3%)	3(9.4%)		42(44.7%)	29(54.7%)	13(31.7%)		**<0.001**	**<0.001**	**0.022**
Overweight (25-29.9)	37(35.2%)	25(34.2%)	12(37.5%)		21(22.3%)	11(20.7%)	10(24.4%)		**0.044**	**0.095**	0.226
Obese (30+)	48(45.7%)	31(42.5%)	17(53.1%)		31(33.0%)	13(24.5%)	18(43.9%)		**0.066**	**0.035**	0.435

[a] Data expressed as n(column %) unless specified; [b] p-value using two sample proportion using column percentage; [c] Females only; [d] Waist:hip ratio classified as normal (< 0.90 in males; < 0.86 in females) or at risk if higher; Bold p values are significant or borderline significant.

Table 2. Lipids, insulin and insulin resistance by T2D status and study site

	Texas-Mexico				South Africa				Texas-Mexico vs South Africa[b]		
	ALL	Type 2 diabetes			ALL	Type 2 diabetes			All	No T2D	T2D
		No T2D	T2D	P		No T2D	T2D	P	P	P	P
Lipid profiles (n, column %) [a]											
Triglycerides				**0.003**				**0.008**	**0.065**	**0.077**	**0.083**
Normal	66(62.3%)	53(71.6%)	13(40.6%)		70(74.5%)	45(84.9%)	25(61.0%)				
High	40(37.7%)	21(28.4%)	19(59.4%)		24(25.5%)	8(15.1%)	16(39.0%)				
Total cholesterol				**0.063**				**0.076**	**<0.001**	**0.003**	**0.019**
Normal	95(89.6%)	69(93.2%)	26(81.3%)		62(66.0%)	39(73.6%)	23(56.1%)				
High	11(10.4%)	5(6.8%)	6(18.8%)		32(34.0%)	14(25.9%)	18(45%)				
LDL				0.404				**0.023**	**0.004**	0.430	**<0.001**
Normal	70(66%)	47(63.5%)	23(71,9%)		41(45.6%)	29(55.8%)	12(31.6%)				
High	36(34%)	27(36.5%)	9(28.1%)		49(54.4%)	23(43.4%)	26(70.3%)				
Male HDL (cut-off = 40)				0.685				**0.010**	**<0.001**	**<0.001**	0.641
Normal	11(31.4%)	8(29.6%)	3(37.5%)		21(77.8%)	18(90%)	3(42.9%)				
Low	24(68.6%)	19(70.4%)	5(62.5%)		6(22.2%)	2(10%)	4(57.1%)				
Female HDL (cut-off = 50)				**0.075**				0.389	0.131	0.180	**0.071**
Normal	28(39.4%)	22(46.8%)	6(25%)		35(52.2%)	19(57.6%)	16(47.1%)				
Low	43(60.6%)	25(53.2%)	18(75%)		32(47.8%)	14(41.2%)	18(54.5%)				
Glucose, HbA1c, insulin and HOMA-IR as estimate of insulin resistance (median, IQR)											
Glucose (mg/dL)	104.5(35)	96.5(20)	167.5(114.5)	**<0.001**	97.3(59.5)	86.5(19.8)	163.1(132.4)	**<0.001**	**0.072**	**<0.001**	0.306
HbA1c (%)	5.7(1.5)	5.5(0.4)	8.0(2.9)	**<0.001**	6.0(2)	5.5(0.7)	7.9(3.5)	**<0.001**	**0.090**	0.683	0.605
Insulin (mU/L) [c]	11.6 (9.2)	11.1 (8.4)	13.6 (9.4)	0.133	11.7(11.9)	9.8(8.9)	15.6(20.5)	**<0.001**	0.960	**0.077**	0.194
HOMA-IR [c]	3.3 (3.2)	2.7 (2.0)	6.7 (4.4)	**<0.001**	2.8 (4.7)	1.9(2.4)	5.9(5.6)	**<0.001**	0.832	**0.017**	0.376

[a] Values in mg/dL; [b] p-value using two sample proportion using column percentage; [c] Data from non-insulin users only; Bold values are significant or borderline significant

19

Figure Legends

Fig 1. Body-mass index and waist-hip ratio in contacts by T2D status and enrollment site. A. Body-mass index was classified as normal, overweight or obese (see methods). B. Waist-hip ratio estimates were categorized into two groups: excellent plus good or average, or at risk, with cut-offs differing by sex (see methods). The proportion of the contacts in each category is shown by T2D status.

Fig 2. Criteria for diagnosis of T2D by study site. T2D diagnosis was based on the current WHO guidelines (see methods). The proportion of contacts fulfilling each criterium for T2D classification is indicated by study site. SR= self-reported only; ↑ Glu = hyperglycemia only; ↑ HbA1c = HbA1c ≥ 6.5% only; ↑ Glu + HbA1c = Both high glucose and HbA1c.

Fig 3. Relationship between adjusted HOMA-IR, BMI and triglycerides. (A) Scatter plot of correlation between adjusted HOMA-IR and triglycerides (mg/dL) by study site. The effect size was d=0.95 for triglycerides*BMI (p <0.001). Analysis was made with ANCOVA with adjustment for site, age, BMI, sex, triglycerides and sex*site, sex*age and BMI*triglycerides. (B and C) Surface plots of the relationships between between adjusted HOMA-IR, BMI and triglycerides in Texas-Mexico and South Africa. In South Africa there were few individuals with triglycerides below 200 mg/dl, computing unstable coefficients and increasing noise in these points.

Fig 4. Dyslipidemia by study site and T2D status. Analysis of covariance contrasts lipid serum concentration (outcomes A-D) by T2D status (no T2D, pre-T2D and T2D) and between sites, after controlling for age and sex. Fisher contrast was used for T2D status as indicator variable (fixed factor), study site (random factor) and the model was adjusted for sex and age. A) Triglycerides were higher in Texas-Mexico (Cohen-d=0.43, p=0.002), and in T2D patients (Cohen-d= 0.44, p=0.003), but not pre-T2D. B) Total cholesterol was higher in South Africa (Cohen-d= 0.67, p=0.0001), but was not affected by T2D status. C) HDL-c was lower in pre-T2D (0.011) and T2D (Cohen-d= 0.43, p=0.006), in Texas-Mexico (Cohen-d= 0.5, p=0.001). D) LDLs had an interaction effect between study site and T2D status (Cohen-d= 0.38, p=0.045).

Vertical lines indicate 95% confidence intervals; Common letters indicate homogenous groups within T2D groups and * indicates differences by study site.

Fig 5. Relationship between variables related to BMI and glucose and lipid metabolism in South Africa and Texas-Mexico. Analysis and visualization of the correlations between variables defining T2D (HbA1c, HOMA-IR), obesity (waist-hip ratio, BMI) and lipid metabolism (LDL-c, HDL-c, triglycerides) by PCA analysis. The Kaiser-Meier-Olkin sampling adequacy was 0.627 for South Africa and 0.5 for Texas-Mexico, and Barttlet's test of sphericity was <0.001 for both sites. A) In South Africa the first two

components (PC 1 with correlated variables HbA1c, HOMA-IR, triglycerides, LDL, and waist-hip ratio, and PC2 with inversely correlated variables BMI and HDL) explained 53% of the variability. B and C) The data from Texas-Mexico required four components (PC1 with triglycerides and HDL-c; PC2 with HOMA-IR and HbA1c; PC3 with waist-hip ratio and BMI; PC4 with LDL-c) to explain 79% of the total variability. Figure C shows the rotated component matrix of B to illustrate the separation of LDL from the other variables. SAfr, South Africa; TxMx, Texas-Mexico.

Supplementary data

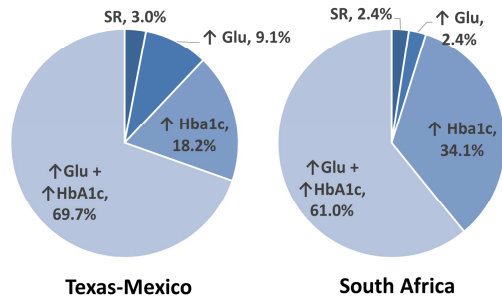Supplementary Table S1

Supplementary Table S2

Supplementary Figure S1
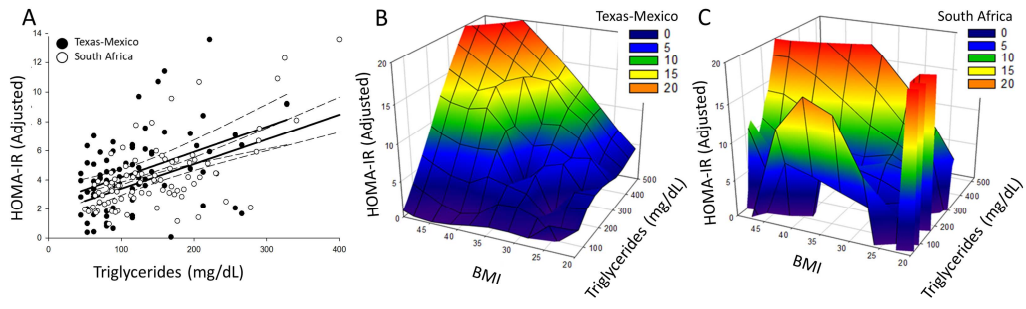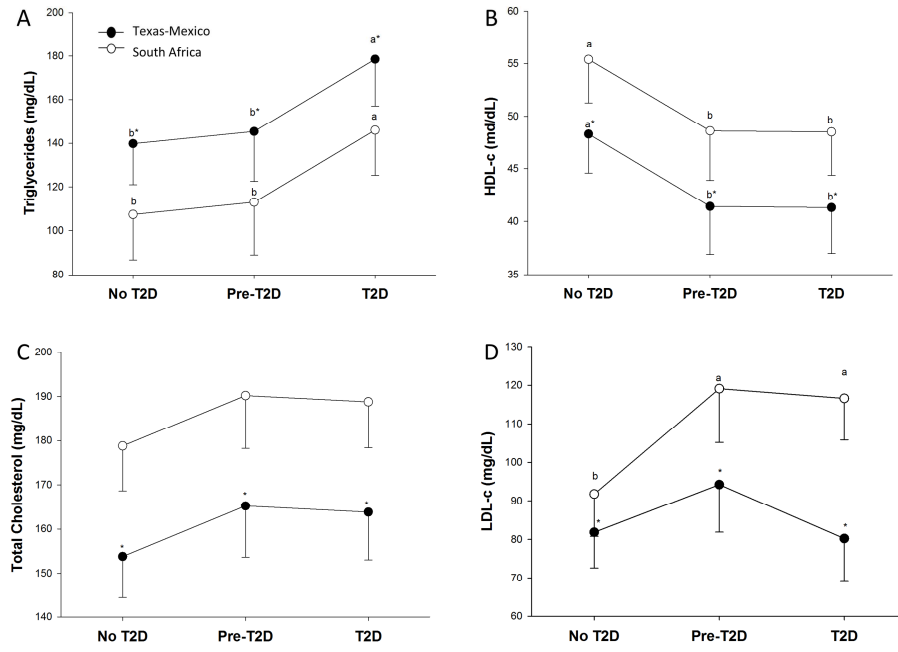
Supplementary Figure S2

A. BMI by T2D status
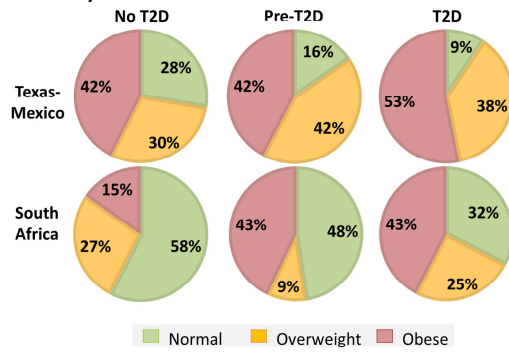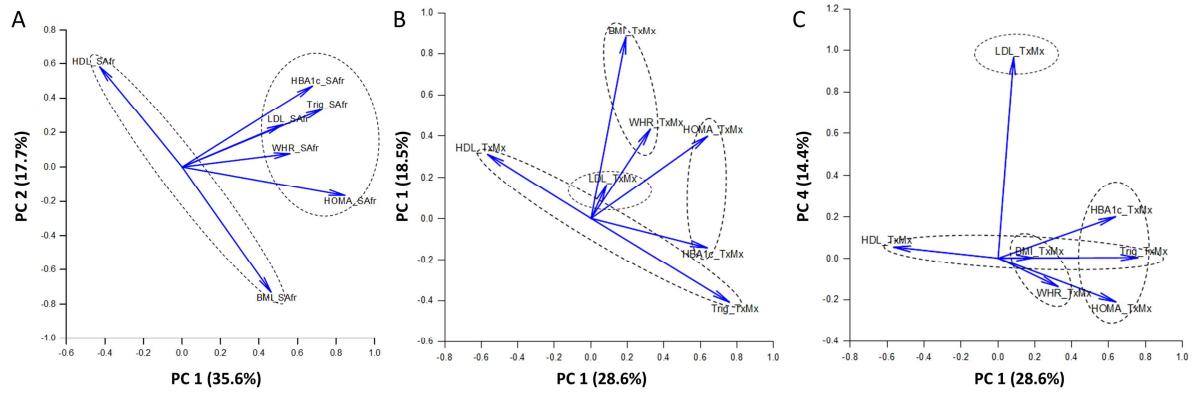

B. Waist-hip ratio by T2D status

SR, 3.0% ↑ Glu, 9.1%

SR, 2.4% ↑ Glu, 2.4%

↑ Hba1c, 18.2%

↑Glu + ↑HbA1c, 69.7%

↑ Hba1c, 34.1%

↑Glu + ↑HbA1c, 61.0%

Texas-Mexico   **South Africa**