Diabetes increases severe COVID-19 outcomes primarily in younger adults Age and diabetes in COVID-19 severity

Marc Diedisheim, Etienne Dancoisne, Jean-François Gautier, Etienne Larger, Emmanuel Cosson, Bruno Fève, Philippe Chanson, Sébastien Czernichow, Sopio Tatulashvili, Marie-Laure Raffin-Sanson, et al.

HAL Id: hal-03246831

https://hal.sorbonne-universite.fr/hal-03246831v1

Submitted on 2 Jun 2021

Diabetes increases severe COVID-19 outcomes primarily in younger adults

Short title: Age and diabetes in COVID-19 severity

Marc Diedisheim[1,2], Etienne Dancoisne[3,4], Jean-François Gautier[1,5], Etienne Larger[2], Emmanuel Cosson[6,7], Bruno Fève[8], Philippe Chanson[9], Sébastien Czernichow[10], Sopio Tatulashvili[11], Marie-Laure Raffin-Sanson[12], Muriel Bourgeon[13], Christiane Ajzenberg[14], Agnès Hartemann[15], Christel Daniel[3,16], Thomas Moreau[17], Ronan Roussel[1,18], Louis Potier[1,18]

1 Cordeliers Research Centre, ImMeDiab team, INSERM, Université de Paris, Paris, France

2 Hospital Cochin, APHP, Diabetology Department, Paris, France. Université de Paris, Paris, France

3 Assistance Publique-Hôpitaux de Paris, DSI WIND, Web Innovation Données, Paris, France

4 Hôpital Bichat - Claude-Bernard, Clinical Research Unit, France

5 GH Lariboisiere Fernand-Widal, AP-HP, Department of Diabetes and Endocrinology, Paris, France. Cordeliers Research Centre, INSERM, ImMeDiab team, Paris, France

6 Hospital Avicenne, APHP, Department of Endocrinology-Diabetology-Nutrition, CRNH-IdF, CINFO, Bobigny, France.

7 Université Sorbonne Paris Cité, UMR U557 INSERM/U11125 INRAE, Unité de Recherche Epidémiologique Nutritionnelle, Bobigny, France

8 Hôpital Saint-Antoine, Department of Endocrinology-Diabetology, APHP, Institut Hospitalo-Universitaire ICAN, Paris, France. Sorbonne Université, INSERM, UMR_S938, CRMR PRISIS, Paris, France

9 Hôpital Bicêtre, APHP, Service d'Endocrinologie et des Maladies de la Reproduction

24   Le Kremlin-Bicetre, France. Université Paris-Saclay, Inserm, Physiologie et Physiopathologie

25   Endocriniennes, Le Kremlin-Bicetre, France

26   10 Hôpital Européen Georges Pompidou Cancérologie, Service de Nutrition, Centre Spécialisé

27   Obésité, Paris, France. Université de Paris, INSERM, UMR1153, Epidemiology and Biostatistics

28   Sorbonne Paris Cité Centre (CRESS), Paris, France

29   11 Hospital Avicenne, AP-HP, Department of Endocrinology-Diabetology-Nutrition Bobigny,

30   France. Université Sorbonne Paris Cité, Epidemiology and Biostatistics Research Center,

31   Nutritional Epidemiology Research Team (EREN), Inserm U1153, INRA U1125 Bobigny,

32   France

33   12 Hospital Ambroise Paré, APHP, Service d'Endocrinologie Diabétologie et Nutrition,

34   Boulogne-Billancourt, France. Université de Versailles Saint-Quentin-en-Yvelines Versailles,

35   France

36   13 Hôpital Antoine-Béclère, APHP, Service de Médecine Interne, Clamart, France

37   14 Hospital Henri Mondor, APHP, Service de Médecine Interne, Creteil, France

38   15 Sorbonne Université, Institute of Cardiometabolism and Nutrition ICAN, Paris, France.

39   University Hospital Pitié Salpêtrière, APHP, Diabetes Department, Paris, France.

40   16 Sorbonne Université, University Paris 13, Sorbonne Paris Cité, INSERM UMR_S 1142,

41   Paris, France

42   17 Université Paris-Saclay, Inria, CEA, Palaiseau, France

43   18 Hôpital Bichat - Claude-Bernard, APHP, Department of Diabetology, Paris, France

44

45   **Corresponding author:**

46   Dr Louis Potier

47   Diabetology, Endocrinology and Nutrition Department, Bichat Hospital, AP-HP

48   46 rue Henri Huchard 75018 Paris

49   tel: + 33 (0) 1 40 25 73 01

50   email: louis.potier@aphp.fr

51

53

54   **DISCLOSURE SUMMARY:** The authors have nothing to disclose.

55

ABSTRACT

Context. Diabetes is reported as a risk factor for severe COVID-19, but whether this risk is similar in all categories of age remains unclear.

Objective. To investigate the risk of severe COVID-19 outcomes in hospitalized patients with and without diabetes according to age categories.

Design Setting and Participants. We conducted a retrospective observational cohort study of 6,314 consecutive patients hospitalized for COVID-19 between February and June 30 2020, and follow-up recorded until 30 September 2020, in the Paris metropolitan area, France.

Main Outcome Measure(s). The main outcome was a composite outcome of mortality and orotracheal intubation in subjects with diabetes compared with subjects without diabetes, after adjustment for confounding variables and according to age categories.

Results. Diabetes was recorded in 39% of subjects. Main outcome was higher in patients with diabetes, independently of confounding variables (HR 1.13 [1.03-1.24]) and increased with age in individuals without diabetes, from 23% for those <50 to 35% for those >80 years but reached a plateau after 70 in those with diabetes. In direct comparison between patients with and without diabetes, diabetes-associated risk was inversely proportional to age, highest in <50 and similar after 70 years. Similarly, mortality was higher in patients with diabetes (26%) than in those without diabetes (22%, p<0.001), but adjusted HR for diabetes was significant only in patients under 50 (HR 1.81 [1.14-2.87]).

Conclusions. Diabetes should be considered as an independent risk factor for the severity of COVID-19 in young adults more so than in older adults, especially for individuals younger than 70 years.

INTRODUCTION

For the past year, the COronaVIrus Disease-2019 (COVID-19) pandemic has spread around the

world leading to more than 2.0 million deaths, with higher risk of severe illness in older adults

and those with comorbidities including diabetes (1, 2), leading to increasing anxiety in this

population. It is becoming increasingly evident that the main risk factor for severe outcomes is

age: elderly people, over 70, had the highest burden of risk associated with COVID-19 (3). In

contrast, diabetes is prevalent in people from a wide range of ages and whether it is associated

with severe outcomes in all age groups is not known. The aim of this study was to compare

severe outcomes among patients with and without diabetes hospitalized for COVID-19 according

to age in a large French repository database.

METHODS

This observational study used the EDS-COVID (Entrepôt de données de santé COVID) database

from the Assistance Publique-Hôpitaux de Paris (AP-HP) Hospitals (regrouping 39 French

public hospitals), aggregating on a daily basis hospitalization-related electronic health records

since the beginning of the COVID-19 epidemic (4). Data for all patients above 18 with

confirmed positive SARS-CoV-2 PCR tested between February 6th (first positive PCR recorded)

and June 30 2020 was retrieved from this database (n=10,448) and patients follow-up was

recorded until 30 September 2020. Patients without available body mass index (BMI) (n=4,134)

were excluded.

This study was approved by the institutional review board from the AP-HP CDW Scientific and

Ethics Committee (IRB 00011591). All subjects included in this study were informed about the

101 reuse of their data for research and subjects that objected to the reuse of their data were excluded

102 in accordance with French legislation.

Comorbidities

104 Chronic comorbidities were extracted using ICD-10 codes in any previous or current

105 hospitalization: C00 to D49 for malignancies, E78 for dyslipidemia, G473 for sleep apnea, I10

106 for high blood pressure, I20 to I25, I63, I64 and I70 to I79 for cardiovascular disease, I50 for

107 heart failure, J44 for chronic obstructive pulmonary disease and N18 for chronic kidney disease.

108 Smoking status was defined as a binary variable by extracting mentions of both current and

109 history of smoking from free-text electronic health records using a dedicated pipeline.

110 Diabetes was defined as being diagnosed a E10 to E14 ICD-10 codes, treatment by an

111 intermediate or long-acting insulin treatment (ATC codes A10AC, A10AD, A10AE) or other

112 non-insulin blood glucose lowering drugs (ATC codes A10B) in any previous or current

113 hospitalization, or having a hemoglobin A1c (HbA1c) level greater than 6.5% (48 mmol/mol) in

114 any previous or current hospitalization. HbA1c within 1 year prior or 7 days after positive PCR

115 result date was available for 1,892 patients.

Primary and Secondary Outcomes

117 The primary outcome was a composite of in-hospital mortality or intensive care unit (ICU)

118 admission with oro-tracheal intubation (OTI) within 90 days of first admission with positive

119 PCR. The secondary outcome was in-hospital mortality at 90 days alone.

Statistical analysis

121 Continuous variables are presented as median (interquartile range) and categorical variables as

122 number (percentage). Baseline characteristics were compared with the two-sided t-test for

123 continuous variables and χ^2 test for categorical variables.

124   Multivariate Cox Proportional Hazards Models assessed the risk of primary and secondary

125   outcomes according to age categories in: *i)* patients with and without diabetes analyzed

126   separately; and *ii)* between patients with and without diabetes. Models included age (except for

127   subgroup analysis), BMI (classes), sex, smoking status and all aforementioned comorbidities.

128   Considering that intermediate or long-acting insulin may be prescribed to treat stress- or

129   glucocorticoid-induced acute hyperglycemia in patients with COVID-19 in order to minimize

130   contact with the patients, we also performed a sensitivity analysis in which we excluded patients

131   for whom diabetes had been defined only by prescription of intermediate or long-acting insulin

132   during hospitalisation. R (https://www.R-project.org/) was used for statistical analysis.

133

134

135   **RESULTS**

136   Among the 6,314 included individuals, 2,459 (39%) had a diagnosis of diabetes. The

137   characteristics of participants at baseline were presented in Table 1. Compared to patients

138   without diabetes, patients with diabetes had comparable age (69 [58-79] *vs* 70 [54-83], p = 0.48),

139   comprised a higher proportion of men (65 *vs* 54%, p <0.001), and presented with higher rate of

140   associated comorbidities: higher BMI (27.4 [23.9-31.2] *vs* 25.3 [22.0-29.3] kg/m², p<0.001),

141   previous arterial hypertension (62 *vs* 43%, p<0.001), dyslipidemia (21 *vs* 8%, p <0.001),

142   cardiovascular diseases (34 *vs* 19%, p <0.001), heart failure (19 *vs* 15%, p <0.001) and chronic

143   kidney disease (26 *vs* 17%, p <0.001).

144   During a 90-day follow-up period from first admission with positive PCR, primary outcome

145   occurred in 2,197 (35%) individuals and increased by age categories from 26% among patients

146   under < 50 to 35% among those over > 80 years. In subgroup analyses according to age and

147   diabetes status, we observed a progressive increased incidence of primary outcomes with age in

148   all age groups in patients without diabetes whereas a plateau was reached from the seventh

149   decade in those with diabetes (Figure 1A).

150   Diabetes was significantly associated with a higher risk of primary outcome (970/2,459, 39%)

151   compared to those without diabetes (1,227/3,855, 32%) with an adjusted hazard ratio (HR) of

152   1.13 [95%CI 1.04-1.25]. The incidence rate difference between people with and without diabetes

153   decreased with age (interaction p-value 0.002, Figure 1A). Accordingly, the adjusted HR for the

154   risk of primary outcome between groups decreased with age from 1.52 [1.18-1.97] for patients

155   under 50 years to 1.30 [1.08-1.57] for patients aged 60-70 years, and was no longer significant

156   for those over 70 (Figure 1B).

157   Similar results were obtained for mortality alone, with a mortality rate higher in patients with

158   diabetes (n=637, 26%) than in those without (n=831, 22%, p< 0.001). Mortality rate increased in

159   both groups with age, but adjusted HR for diabetes remained significant only in patients under 50

160   (HR 1.81 [1.14-2.87]).

161   In sensitivity analysis without inclusion of patients with diabetes defined only by prescription of

162   intermediate or long-acting insulin during hospitalization, we found similar results for primary

163   outcomes and mortality in the whole population (adjusted HR for the risk of primary outcome:

164   1.10 [95%CI 1.01-1.21]) and for each age category: in patients under 50, the adjusted HR for the

165   risk of primary outcome is 1.45 [1.11-1.89] but was no longer significant for those over 70 (1.03

166   [95%CI 0.85-1.23]).

167

168   **DISCUSSION**

169 In this cohort of 6,314 patients hospitalized for COVID-19, we found that diabetes was an

170 independent factor of severe outcomes after adjustment for comorbidities. In subgroup analyses

171 by age categories, we showed that increasing age tends to alleviate the higher risk of severity

172 observed in patients with diabetes compared to patients without diabetes.

173 Trends in COVID-19 deaths by age have been clear since early in the pandemic with a risk of

174 death increasing from the age of 50 (1, 3, 5). Older people, especially after 70 years, are facing

175 the highest burden of COVID-19 mortality (6). Beyond age, people living with diabetes have

176 been identified as people at high risk. However, whether diabetes is an independent factor for

177 severe outcomes remains unclear (2, 7–10). Here, in the whole population of analysis, we found

178 that diabetes was associated with a higher risk of severe outcomes after adjustment for

179 confounders. However, diabetes-associated risk was only observed in the younger categories of

180 age suggesting that diabetes should be considered as an independent risk factor for severity

181 mainly in people under 70 years and, even more so, among those under 50 years. In line with our

182 findings, a recent meta-analysis found that the increased diabetes related mortality was

183 attenuated in older patients (11). Similarly, Gregory *et al.* reported that risk of hospitalization for

184 COVID-19 according to age increased from the 5th decade of age in subjects with no diabetes

185 while the risk increased from 20 to 50 and then reached a plateau in those with type 2 diabetes

186 (12). Deduced from their figure, the highest difference between HR for hospitalization of people

187 with diabetes and no diabetes was in the sixth decade. Moreover, Legris et al has recently shown

188 that diabetes is not associated with COVID-19-related mortality in older institutionalized people

189 (13). Taken together, these results might suggest that over 50, diabetes-related risk is weakened

190 by all other comorbidities or conditions associated with age. These findings are consistent with

191 previous observational data in the general population of type 2 diabetes, beyond the scope of

192   COVID-19, showing that diabetes-associated risk of death decreased in a stepwise fashion from

193   younger to older age groups (14).

194   One strength of our study is the number of patients included, covering a wide range of

195   individuals hospitalized for COVID-19 in the same area, while associated with detailed clinical

196   information. On the other hand, there are several limitations. First, glucose-lowering treatment

197   prior to and given during hospitalization was not known. Furthermore, type of diabetes was not

198   reliably indicated, making it impossible to determine which type of diabetes is associated with a

199   poor prognosis. Similarly, no information regarding the duration of diabetes is available in our

200   study. However, duration of diabetes has not been shown to be associated with poor prognosis in

201   patients with diabetes hospitalized for COVID-19 (15). Finally, since out-of-hospital deaths were

202   not recorded in our data, we cannot exclude that this unavailable information may have impacted

203   our results.

204   To conclude, our study suggests physicians dealing with SARS-CoV-2 infected subjects should

205   consider diabetes as an independent risk factor for the severity of COVID-19 in young adults

206   more so than in older adults.

207

215 **Data Availability**

216 Restrictions apply to the availability of some or all data generated or analyzed during this study

217 to preserve patient confidentiality or because they were used under license. The corresponding

218 author will on request detail the restrictions and any conditions under which access to some data

219 may be provided.

223 **Duality of interest**

224 All authors had no conflict of interest to disclose related to this work.

225 **Authors contributions**

226 M.D. designed the study, conducted analysis and wrote the manuscript. E.D. structured the

227 database, conducted analysis and wrote the manuscript. L.P. designed the study, conducted

228 analysis and wrote the manuscript. Critical revision of the manuscript for important intellectual

229 content: all authors. L.P. had full access to all the data in the study and takes responsibility for

230   the integrity of the data and the accuracy of the data analysis. The corresponding author attests

231   that all listed authors meet authorship criteria and that no others meeting the criteria have been

232   omitted.

233

234

REFERENCES

236 1. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, Tobin KA, Cerfolio
237 RJ, Francois F, Horwitz LI. Factors associated with hospital admission and critical illness among
238 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. BMJ
239 2020;369:m1966.

240 2. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read
241 JM, Dondelinger F, Carson G, Merson L, Lee J, Plotkin D, Sigfrid L, Halpin S, Jackson C,
242 Gamble C, Horby PW, Nguyen-Van-Tam JS, Ho A, Russell CD, Dunning J, Openshaw PJM,
243 Baillie JK, Semple MG. Features of 20 133 UK patients in hospital with covid-19 using the
244 ISARIC WHO Clinical Characterisation Protocol: Prospective observational cohort study. BMJ
245 2020;369:m1985.

246 3. Perez-Saez J, Lauer SA, Kaiser L, Regard S, Delaporte E, Guessous I, Stringhini S, Azman
247 AS, Alioucha D, Arm-Vernez I, Bahta S, Barbolini J, Baysson H, Butzberger R, Cattani S,
248 Chappuis F, Chiovini A, Collombet P, Courvoisier D, De Ridder D, De Weck E, D'ippolito P,
249 Daeniker A, Desvachez O, Dibner Y, Dubas C, Duc J, Eckerle I, Eelbode C, El Merjani N,
250 Emery B, Favre B, Flahault A, Francioli N, Gétaz L, Gilson A, Gonul A, Guérin J, Hassar L,
251 Hepner A, Hovagemyan F, Hurst S, Keiser O, Kir M, Lamour G, Lescuyer P, Lombard F, Mach
252 A, Malim Y, Marchetti E, Marcus K, Maret S, Martinez C, Massiha K, Mathey-Doret V, Mattera
253 L, Matute P, Maugey JM, Meyer B, Membrez T, Michel N, Mitrovic A, Mohbat EM, Nehme M,
254 Noël N, Oulevey HK, Pardo F, Pennacchio F, Petrovic D, Picazio A, Piumatti G, Pittet D, Portier
255 J, Poulain G, Posfay-Barbe K, Pradeau JF, Pugin C, Rakotomiaramanana RB, Richard A,
256 Rocchia Fine C, Sakvarelidze I, Salzmann-Bellard L, Schellongova M, Schrempft S, Seixas
257 Miranda M, Stimec M, Tacchino M, Theurillat S, Tomasini M, Toruslu KG, Tounsi N, Trono D,
258 Vincent N, Violot G, Vuilleumier N, Waldmann Z, Welker S, Will M, Wisniak A, Yerly S,
259 Zaballa ME, Zeballos Valle A. Serology-informed estimates of SARS-CoV-2 infection fatality
260 risk in Geneva, Switzerland. Lancet Infect. Dis. 2021;21(4):e69-e70.

261 4. Czernichow S, Beeker N, Rives-Lange C, Guerot E, Diehl JL, Katsahian S, Hulot JS,
262 Poghosyan T, Carette C, Jannot AS. Obesity Doubles Mortality in Patients Hospitalized for
263 Severe Acute Respiratory Syndrome Coronavirus 2 in Paris Hospitals, France: A Cohort Study
264 on 5,795 Patients. Obesity (Silver Spring). 2020;28(12):2282–2289.

265 5. Pastor-Barriuso R, Pérez-Gómez B, Hernán MA, Pérez-Olmeda M, Yotti R, Oteo-Iglesias J,
266 Sanmartín JL, León-Gómez I, Fernández-García A, Fernández-Navarro P, Cruz I, Martín M,
267 Delgado-Sanz C, Fernández De Larrea N, León Paniagua J, Muñoz-Montalvo JF, Blanco F,
268 Larrauri A, Pollán M. Infection fatality risk for SARS-CoV-2 in community dwelling population
269 of Spain: Nationwide seroepidemiological study. BMJ 2020;371:m4509.

270 6. Ward H, Atchison C, Whitaker M, Ainslie KEC, Elliott J, Okell L, Redd R, Ashby D,
271 Donnelly CA, Barclay W, Darzi A, Cooke G, Riley S, Elliott P. SARS-CoV-2 antibody
272 prevalence in England following the first peak of the pandemic. Nat. Commun. 2021;12(1):1–8.

273   7. Xu J, Yang X, Yang L, Zou X, Wang Y, Wu Y, Zhou T, Yuan Y, Qi H, Fu S, Liu H, Xia J, Xu
274   Z, Yu Y, Li R, Ouyang Y, Wang R, Ren L, Hu Y, Xu D, Zhao X, Yuan S, Zhang D, Shang Y.
275   Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19:
276   A multicenter retrospective study from Wuhan, China. Crit. Care 2020;24(1):394.

277   8. Sutter W, Duceau B, Vignac M, Bonnet G, Carlier A, Roussel R, Trimaille A, Pommier T,
278   Guilleminot P, Sagnard A, Pastier J, Weizman O, Giordano G, Cellier J, Geneste L, Panagides
279   V, Marsou W, Deney A, Karsenty C, Attou S, Delmotte T, Ribeyrolles S, Chemaly P, Gautier A,
280   Fauvel C, Chaumont C, Mika D, Pezel T, Cohen A, Potier L. Association of diabetes and
281   outcomes in patients with COVID-19: Propensity score-matched analyses from a French
282   retrospective cohort. Diabetes Metab. 2020;47(4):101222.

283   9. de Jong M, Woodward M, Peters SAE. Diabetes and COVID-19–related mortality in women
284   and men in the UK biobank: Comparisons with influenza/ pneumonia and coronary heart disease.
285   Diabetes Care 2021;44(2):e22–e24.

286   10. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, Knighton P, Holman N, Khunti
287   K, Sattar N, Wareham NJ, Young B, Valabhji J. Associations of type 1 and type 2 diabetes with
288   COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol.
289   2020;8(10):813–822.

290   11. Corona G, Pizzocaro A, Vena W, Rastrelli G, Semeraro F, Isidori AM, Pivonello R, Salonia
291   A, Sforza A, Maggi M. Diabetes is most important cause for mortality in COVID-19 hospitalized
292   patients: Systematic review and meta-analysis. Rev. Endocr. Metab. Disord. 2021;22(2):275-
293   296.

294   12. Gregory JM, Slaughter JC, Duffus SH, Smith TJ, LeStourgeon LM, Jaser SS, McCoy AB,
295   Luther JM, Giovannetti ER, Boeder S, Pettus JH, Moore DJ. COVID-19 Severity Is Tripled in
296   the Diabetes Community: A Prospective Analysis of the Pandemic's Impact in Type 1 and Type
297   2 Diabetes. Diabetes Care 2021;44(2):526-532.

298   13. Legris P, Vaillard L, Nonciaux C, Hourdain P, Taroux M, Petit J-M, Vergès B, Bouillet B.
299   Diabetes is not associated with COVID-19-related mortality in older institutionalized people.
300   Diabetes Metab. 2021;47(3):101235.

301   14. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson A-M, Miftaraj M, McGuire DK,
302   Sattar N, Rosengren A, Gudbjörnsdottir S. Mortality and Cardiovascular Disease in Type 1 and
303   Type 2 Diabetes. N. Engl. J. Med. 2017;376(15):1407–1418.

304   15. Wargny M, Potier L, Gourdy P, Pichelin M, Amadou C, Benhamou PY, Bonnet JB, Bordier
305   L, Bourron O, Chaumeil C, Chevalier N, Darmon P, Delenne B, Demarsy D, Dumas M, Dupuy
306   O, Flaus-Furmaniuk A, Gautier JF, Guedj AM, Jeandidier N, Larger E, Le Berre JP, Lungo M,
307   Montanier N, Moulin P, Plat F, Rigalleau V, Robert R, Seret-Bégué D, Sérusclat P, Smati S,
308   Thébaut JF, Tramunt B, Vatier C, Velayoudom FL, Vergès B, Winiszewski P, Zabulon A,
309   Gourraud PA, Roussel R, Cariou B, Hadjadj S. Predictors of hospital discharge and mortality in
310   patients with diabetes and COVID-19: updated results from the nationwide CORONADO study.
311   Diabetologia 2021;64(4):778–794.

FIGURE LEGENDS

313 **Figure 1**: Orotracheal intubation and mortality risk in patients with COVID-19 according to

314 diabetes status. Five age categories are shown on the y-axis. A: primary composite outcome

315 reported as percentage for patients with (grey circles) or without (black circles) diabetes. B:

316 corresponding multi-adjusted hazard ratio and confidence-interval 95% for presence of diabetes

317 compared with no diabetes within each age category. HR: Hazard ratio.

318

319

320   **Table 1: Baseline characteristics of participants**

	No Diabetes (n = 3855)	**Diabetes (n = 2459)**	**P-value**
Age (years)	70 (54-83)	69 (58-79)	0.476
Sex: Female	1760 (46)	866 (35)	<0.001
BMI	25 (22-29)	27 (24-31)	<0.001
Smoking	617 (16)	470 (19)	0.001
Hypertension	1656 (43)	1513 (62)	<0.001
CVD	739 (19)	825 (34)	<0.001
Heart Failure	567 (15)	470 (19)	<0.001
Renal Failure	648 (17)	650 (26)	<0.001
COPD	281 (7)	166 (7)	0.416
Dyslipidemia	326 (8)	523 (21)	<0.001
Sleep Apnea	199 (5)	256 (10)	<0.001

321

322   Median (Interquartile) or n (%). BMI: body mass index, CVD: cardiovascular disease, COPD:
323   chronic obstructive pulmonary disease