Matched population-based study examining the risk of type 2 diabetes in people with and without diagnosed hepatitis C virus infection

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1 Title:

2 Matched population-based study examining the risk of type 2 diabetes in
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35 Matched population-based study examining
36 the risk of type 2 diabetes in people with and
37 without diagnosed hepatitis C infection

38 **Abstract**

39 Meta-analyses have found hepatitis C virus (HCV) infection to be
40 associated with an increased risk of type 2 diabetes mellitus (T2DM).
41 Here, we examine this association within a large population-based study,
42 according to RNA status.

43 A data-linkage approach was used to examine the excess risk of
44 diagnosed T2DM in people diagnosed with HCV-antibodies in Scotland
45 (21,929 Ab^{+ves} ; involving 15,827 RNA^{+ves} , 3927 RNA^{-ves} and 2175
46 with unknown RNA-status) compared to that of a three-fold larger
47 general population sample matched for sex, age and postcode (65,074
48 Ab^{-ves}). To investigate effects of ascertainment bias the following
49 periods were studied: up to one year before (*pre*-HCV)/within one year
50 of (*peri*-HCV)/more than one year post (*post*-HCV) the date of
51 HCV-diagnosis.

52 T2DM had been diagnosed in 2.9% of Ab^{+ves} (including 3.2% of
 53 RNA^{+ves} and 2.3% of RNA^{-ves}) and 2.7% of Ab^{-ves} . A higher proportion
 54 of T2DM was diagnosed in the *peri*-HCV period (i.e. around the time of
 55 HCV-diagnosis) for the Ab^{+ves} (22%) compared to Ab^{-ves} (10%). In
 56 both the *pre*-HCV and *post*-HCV periods, only those Ab^{+ves} living in
 57 less deprived areas (13% of the cohort) were found to have a significant
 58 excess risk of T2DM compared to Ab^{-ves} (adjusted odds ratio in the
 59 *pre*-HCV period: 4.0 for females and 2.3 for males; adjusted hazard ratio
 60 in the *post*-HCV period: 1.5). These findings were similarly observed for
 61 both RNA^{+ves} (chronic) and RNA^{-ves} (resolved).

62 In the largest study of T2DM among chronic HCV-infected individuals
 63 to date, there was no evidence to indicate that infection conveyed an
 64 appreciable excess risk of T2DM at the population level.

65

66 **Keywords:**

67 Hepatitis C, Type 2 Diabetes, Matched cohort study, Data linkage

68 **1 Introduction**

69 A large consistent body of evidence from several observational studies
 70 suggests that Hepatitis C virus (HCV) infection is associated with

71 insulin resistance (IR) and Type 2 diabetes mellitus (T2DM (1-4). In
72 addition, several plausible pathways have been suggested to explain how
73 HCV influences IR and T2DM) (5-7). However, estimates of the size of
74 the effect of HCV on T2DM risk vary between different studies. Two
75 different meta-analyses of a total of 47 different studies both showed
76 approximately 70% increased odds/hazards of having diabetes for
77 individuals with HCV infection compared to individuals without HCV
78 infection (adjusted Odds Ratio (OR), 1.7; 95% Confidence Interval (CI),
79 1.2-2.5 (3) ; and 1.7; 95% CI, 1.2-2.2 (8)). A recent population based
80 cross sectional study from the US (9), however, found little evidence of
81 increased risk to test diabetes positive in people with, compared to
82 without, either current HCV-infection (OR, 1.1; 95% CI, 0.6-1.9) or
83 with current or past HCV-infection (OR, 1.0; 95% CI, 0.6-1.7). In
84 addition, a large population based cohort study from Southern Italy
85 showed that compared to HCV^{-ve} controls only people with HCV and
86 elevated alanine aminotransferase (ALT) levels were at higher odds of
87 developing T2DM (OR, 1.5; 95% CI, 1.0-2.2), while those with HCV
88 and normal baseline ALT levels were at lower odds (OR, 0.6; 95% CI,
89 0.3-1.1) (10). Another study of people enrolled in a community-based
90 cohort in the US showed that HCV infection increased the risk of
91 developing diabetes (adjusted hazard ratio (HR), 11.6; 95%CI 1.4-96.6),

92 but only among those at high risk of diabetes (based on body mass index
93 and age) (11). Finally, a recent meta analysis suggested, on the basis of
94 limited evidence, that having diabetes can also be a risk factor for
95 contracting HCV (12).

96 The heterogeneity of findings from the different studies indicates
97 that, at a population level, the effect of HCV on T2DM risk is
98 comparably low and varies between different strata of the population.
99 Therefore, studies to estimate the size of the effect of HCV on T2DM in
100 the general population need to be sufficiently large to allow examination
101 of different strata of the population and need careful control of
102 confounding. Factors that increase the risk for diabetes and that might
103 differ between those with HCV and those without HCV include low
104 socioeconomic status (13,14), a history of heroin dependence (15) and
105 methadone treatment (16), high alcohol consumption (17), smoking
106 (18), increasing age (19), male sex (19), non white ethnicity (20) and
107 higher body mass index (14).

108 To study the relationship between HCV infection and T2DM at a
109 population level, we compared the risk of T2DM diagnosis in all people
110 who have been diagnosed HCV antibody^{+ve} with the risk of T2DM
111 diagnosis in a three-times larger cohort of controls matched for the
112 major confounding factors of sex, neighbourhood and age. To ascertain

113 whether any difference in the risk of T2DM was related to the virus itself
 114 or to factors associated with HCV-infection, we compared the
 115 relationship between HCV infection and T2DM in all people who had
 116 tested (i) HCV antibody^{+ve}, (ii) HCV antibody^{+ve} and RNA^{+ve} and (iii)
 117 HCV antibody^{+ve} and RNA^{-ve}. To reduce the potential effect of
 118 ascertainment bias associated with being diagnosed for HCV infection,
 119 we studied three different periods of T2DM diagnosis: (i) a diabetes
 120 diagnosis at least 1 year *prior* to HCV diagnosis; (ii) within ± 1 year of
 121 HCV diagnosis and; (iii) later than one year *post* HCV diagnosis.

122 **Patients and Methods**

123 **Data sources for diagnosis of HCV and T2DM**

124 Scotland has comprehensive national disease databases of people
 125 diagnosed with HCV-antibodies and of people diagnosed with diabetes.
 126 The database of people diagnosed with HCV-antibodies held at Health
 127 Protection Scotland holds information on more than 30,000 people from
 128 all over Scotland who have tested HCV antibody^{+ve} between 1985 and
 129 2011 (see (21) for a description of the database). The Scottish Care
 130 Information – Diabetes Collaboration (SCI-DC) manages a national
 131 register that holds information on individuals with diagnosed diabetes

132 (over 300,000) in Scotland and is estimated to have included over 99%
 133 of people with diagnosed diabetes since 2004. Individuals are included
 134 on SCI-DC if they have a Read code¹ for diabetes assigned in primary
 135 care or if they are seen in a hospital diabetes clinic (for a description of
 136 the database, see (22)).

137 **HCV antibody^{+ve} cohort**

138 For the period up to the end of 2011, 31,468 records of HCV antibody^{+ve}
 139 people from all over Scotland were held in the HCV diagnoses database.
 140 From the database, information was extracted on forename initial, a
 141 soundex encrypted version of the surname (soundex is a phonetic
 142 algorithm for indexing names by sound, as pronounced in English), date
 143 of birth, sex, RNA test results at first diagnosis (positive, negative,
 144 unknown) and date of first HCV^{+ve} antibody test (hereafter referred to as
 145 date of HCV diagnosis).

146 To enable linkage of the partially anonymised data in the HCV
 147 database to other databases, 24,975 (79%) records from the HCV
 148 database were probabilistically linked to the database of the community
 149 health index (CHI), a unique identifier used in medical records (23).

¹ Read codes are the standard clinical terminology system used in General Practice in the United Kingdom.

150 After linkage, information from CHI was added to the HCV antibody^{+ve}
 151 cohort including full personal identifiers, postcode sector of residence at
 152 the time of HCV diagnosis, an indicator for social deprivation of the area
 153 of residence (Scottish Index of Multiple Deprivation, SIMD) (24) and an
 154 indicator and date for migration from Scotland. We then excluded 107
 155 people younger than 16 and a total of 588 individuals with missing or
 156 unclear information on SIMD, sex and diagnosis date. After these
 157 exclusions, 24,280 individuals remained in the study population (see
 158 Figure 1 in the Appendix).

159 **HCV antibody^{-ve} cohort**

160 For every person in the HCV antibody^{+ve} cohort, up to three people were
 161 randomly sampled without replacement from the CHI database who
 162 were (i) born within one calendar year; (ii) of the same sex; (iii) alive at
 163 the time of diagnosis of the matched person on the HCV database; (iv)
 164 lived in the same postcode sector (but not in the same postcode) at the
 165 time of HCV diagnosis; and (v) were not included in the HCV
 166 antibody^{+ve} cohort. Given the low prevalence of HCV in the Scottish
 167 population (25), less than 2% of the HCV antibody^{-ve} cohort will likely
 168 have undiagnosed HCV-infection; thus, this misclassification will have
 169 negligible influence on the results. For 2118 people in the HCV

170 antibody^{+ve} cohort, no matching individual could be identified in the
171 CHI database; these people were excluded from the HCV antibody^{+ve}
172 cohort. As a result, 22,162 matched groups were available for analysis.
173 People in the HCV antibody^{-ve} cohort were assigned an index date
174 which corresponded to the diagnosis date of their matched cohort
175 member.

176 **Diabetes**

177 To identify diagnosed diabetes status in both cohorts (HCV antibody^{+ve}
178 and HCV antibody^{-ve}), data were deterministically linked to the
179 SCI-DC database based on CHI number. After linkage, information
180 from SCI-DC was added to the data including type of diabetes (T1DM,
181 T2DM and other/unknown) and date of diabetes diagnosis. For 11 HCV
182 antibody^{+ve} people, diabetes was diagnosed but date of diabetes
183 diagnosis was not available; these individuals, together with their 31
184 matched individuals from the HCV antibody^{-ve} cohort, were removed
185 from analysis. An additional three individuals from the HCV
186 antibody^{-ve} cohort with a diabetes diagnosis were removed as they had
187 no date for their diagnosis. A further 219 HCV antibody^{+ve} individuals
188 were removed together with 652 matched individuals from the HCV

189 antibody^{-ve} cohort because they had been diagnosed with a type of
 190 diabetes other than T2DM. Additionally, 451 people from the HCV
 191 antibody^{-ve} cohort were excluded because they had been diagnosed with
 192 a type of diabetes other than T2DM.

193 **Morbidity and mortality**

194 To identify further censoring dates in both cohorts, data were then linked
 195 deterministically to mortality data from the General Registrars Office of
 196 Scotland (GRO, see (26) for a description of the database) and the date
 197 of death was added to the cohort data. Cohort members were
 198 additionally linked deterministically to hospital databases, to ascertain
 199 whether, prior to the HCV-diagnosis date, they had been in hospital for
 200 an alcohol-related admission (ICD9: 571.[0-3], 291.[0-9], 535.3, 425.5,
 201 357.5, 305.0, 303.9; ICD10: E24.4, E51.2, F10.[0-9], G31.2, G62.1,
 202 G72.1, I42.6, K29.2, K70.[0-9], K86.0, O35.4, P04.3, Q86.0, R78.0,
 203 T51.[0,1,9], X[4,6]5, Y15, Y57.3, Y90.[3-8], Y91, Z50.2, Z71.4, Z72.1)
 204 or for an obesity-related admission (ICD9: 278.[0-9]; ICD10: E66).
 205 Three members of the HCV antibody^{+ve} cohort matched to two different
 206 death records and were subsequently removed from analysis, leaving
 207 21,929 for analysis (Fig. 1).

208 **Information Governance**

209 Data linkages were approved by the NHS National Services Scotland
 210 Privacy Advisory Committee and use of the CHI database was approved
 211 by the CHI Advisory Group. All linkages were undertaken at
 212 Information Service Division, Scotland and all personal identifiable
 213 information removed from the outputs *prior* to release of data to the
 214 research team for analysis.

215 **Statistical analysis**

216 The probability of T2DM diagnosis for those in the HCV antibody^{+ve}
 217 compared to the HCV antibody^{-ve} cohort was determined for the
 218 following three time periods: i) up-to one year before HCV diagnosis
 219 (*pre-HCV*); ii) from one year before HCV diagnosis to one year after
 220 HCV diagnosis (*peri-HCV*); and iii) from one year after HCV diagnosis
 221 to the earlier of either the end of follow-up (November 1st, 2011), death,
 222 migration out of Scotland or diagnosis of T2DM (*post-HCV*).

223 Generalized linear mixed models (R, package lme4) were used for
 224 the analysis of the odds of T2DM diagnosis *pre-HCV* and *peri-HCV*.
 225 Mixed effects Cox models (R, package coxme) were used for the
 226 analysis of the hazard of T2DM diagnosis *post-HCV*. In all three
 227 regression models, the year of HCV diagnosis (grouped into prior to

228 2000 and later than 1999), sex, social deprivation (grouped into three
229 groups using the original quintiles: 1-2=high, 3=medium and 4-5=low
230 deprivation) and age at HCV diagnosis were included as explanatory
231 variables. Fractional polynomials were used to model age at HCV
232 diagnosis (R, package mfp). To adjust for correlation within matched
233 groups, a random group effect was added to all three models.

234 To study if the estimated effect of HCV-infection on the probability
235 of T2DM diagnosis was modified by period of HCV diagnosis, sex,
236 social deprivation or age at HCV diagnosis, interaction-terms between
237 these variables and HCV were added to the full model. Likelihood ratio
238 tests were used for testing the statistical significance of interaction terms
239 and those interaction terms that were not statistically significant
240 ($P>0.05$) were removed. For statistically significant interaction terms, a
241 synergy index (S) was calculated to demonstrate the excess risk from
242 exposure (to both exposures) when there is interaction relative to the risk
243 from exposure (to both exposures) without interaction. Influential
244 values, outliers and model fit were ascertained in the final models
245 excluding random group effects (R, package boot). The assumption of
246 proportionality of hazards in the survival analysis was tested using
247 Schoenfeld residuals (R, package survival).

248 To study the effect of chronic and resolved HCV infection, all final
 249 models were re-run separately for those in the HCV antibody^{+ve} cohort
 250 who were initially tested (i) RNA-positive (indicative of chronic HCV)
 251 and (ii) RNA-negative (indicative of resolved HCV). Here, the HCV
 252 antibody^{-ve} cohorts were composed only of people who were matched
 253 to RNA-positive (for (i)) and RNA-negative (for (ii)) individuals.

254 **Results**

255 **Characteristics of the study population**

256 Table 1 shows the composition of the study population comprising
 257 21,929 people in the HCV antibody^{+ve} cohort and 65,074 people in the
 258 matched HCV antibody^{-ve} cohort. Reflecting the composition of the
 259 HCV antibody^{+ve} population in Scotland, people in the HCV
 260 antibody^{+ve} cohort were predominantly male (68%), born between 1960
 261 and 1980 (68%), were diagnosed with HCV after the year 2000 (70%)
 262 and were living at the time of HCV diagnosis in areas of highest
 263 deprivation (75%). 72% of the people in the HCV antibody^{+ve} cohort
 264 were HCV-RNA^{+ve}, 18% were HCV-RNA^{-ve} and in 10% the RNA
 265 status was unknown. More than 97% of people in the HCV antibody^{+ve}

266 cohort could be matched to three HCV antibody^{-ve} people from the CHI
267 database, while for people born before 1950 fewer matches were
268 identified.

269 Median follow-up time from HCV-diagnosis to censoring or end of
270 follow-up was 6.4 years in the HCV antibody^{+ve} cohort and 6.6 years in
271 the HCV antibody^{-ve} cohort; median age at HCV diagnosis was 33
272 years. During a total follow-up period of 151,020 person-years from
273 HCV-diagnosis to censoring in the HCV antibody^{+ve} cohort, 4016
274 people died (2.66 per 100 person-years). In the HCV antibody^{-ve} cohort,
275 the total follow-up period was 463,977 person-years with 2633 deaths
276 recorded (0.57 per 100 person-years). The proportion of people who
277 have had an alcohol-related hospitalization prior to HCV-diagnosis was
278 considerably higher in the HCV antibody^{+ve} cohort (22%) than in the
279 HCV antibody^{-ve} cohort (4.5%), while there was not much difference in
280 the proportion of people who have had an obesity-related hospitalization
281 (both 0.3%) prior to HCV-diagnosis.

282 **Diagnosis of T2DM in the HCV antibody^{+ve} cohort compared to the**
 283 **HCV antibody^{-ve} cohort**

284 Of 21,929 people in the HCV antibody^{+ve} cohort, 628 (2.86%) had been
 285 diagnosed with T2DM, of whom 187 (30%) had been diagnosed with
 286 T2DM more than a year before they had been diagnosed HCV-positive
 287 and 141 (22%) had been diagnosed with T2DM within one calendar year
 288 of their HCV diagnosis (Table 2). This compares to 1772 out of 65,074
 289 (2.72%) in the HCV antibody^{-ve} cohort who have been diagnosed with
 290 T2DM, of whom 524 (30%) had been diagnosed with T2DM more than
 291 a year before the matched person in the HCV antibody^{+ve} cohort had
 292 been diagnosed HCV-positive and 184 (10%) had been diagnosed with
 293 T2DM within one calendar year of their HCV diagnosis (Table 2). The
 294 difference between both cohorts in the proportion of people who were
 295 diagnosed with T2DM (0.14%) indicates an excess of 32 cases in HCV
 296 antibody^{+ve} study population or 14 per 10,000 HCV-infected people,
 297 while for those who tested RNA^{+ve} and RNA^{-ve}, excess risks of 34 and
 298 20 per 10,000, respectively, were found. In both HCV antibody^{+ve} and
 299 HCV antibody^{-ve} cohorts the median age at diagnosis with T2DM was
 300 45 years.

301 **Odds of T2DM diagnosis up to one year *prior* to HCV diagnosis**

302 In the HCV antibody^{-ve} cohort, male sex and high social deprivation
 303 were associated with increased risks of having a diagnosis of T2DM in
 304 the period up to one year *prior* to HCV diagnosis. However, in the HCV
 305 antibody^{+ve} cohort, the same variables were associated with decreased
 306 risk (Table 3). The 4345 women in the HCV antibody^{-ve} cohort who
 307 resided in areas of lowest deprivation had the lowest risk of having a
 308 diagnosis of T2DM (0.4%), while the 941 women in the HCV
 309 antibody^{+ve} cohort who resided in areas of lowest deprivation had the
 310 highest risk (2.4%; OR, 4.02; 95% CI, 2.29-7.04 $P<0.01$). The 28,267
 311 men in the HCV antibody^{-ve} cohort who resided in areas of highest
 312 deprivation had a higher risk of having a diagnosis of T2DM (0.9%) than
 313 the 11,131 men in the HCV antibody^{+ve} cohort who resided in areas with
 314 the same high deprivation (0.5%; OR, 0.61; 95% CI, 0.43-0.87 $P<0.01$).
 315 The synergy indices show negative interaction on an additive scale,
 316 indicating that the combined effects of male sex and HCV-infection and
 317 deprivation and HCV-infection were less than the sum of the effects of
 318 male sex and HCV-infection and deprivation and HCV-infection.

319 Similar ORs were estimated when restricting the HCV-positive
 320 cohort to either only people who have tested RNA^{+ve} (indicative of

321 chronic infection) or those who have tested RNA-negative (indicative of
322 past infection; Table 3).

323 **Odds of T2DM diagnosis within $\pm$ one year of HCV diagnosis**

324 In the HCV antibody^{-ve} cohort, male sex was associated with increased
325 risks of having a diagnosis of T2DM in the period within one year of
326 HCV diagnosis. However, in the HCV antibody^{+ve} cohort, there was
327 little difference between men and women (Table 4). The lowest risk of
328 having a diagnosis of T2DM was observed for the 20,626 women in the
329 HCV antibody^{-ve} cohort (0.2%) while the highest risk was observed for
330 the 6996 women in the HCV antibody^{+ve} cohort (0.7%; OR, 3.78; 95%
331 CI, 2.29-6.24 $P<0.01$). Increased risks of having a diagnosis of T2DM
332 were also observed in the 14,746 men in the HCV antibody^{+ve} cohort
333 (0.6%) compared to men in the HCV antibody^{-ve} cohort (0.3%), but
334 because of the increased risk in males in the HCV antibody^{-ve} cohort,
335 the estimated adjusted OR was lower than in women (OR, 1.97; 95% CI,
336 1.46-2.65; $P<0.01$). Again, the synergy index indicates negative
337 interaction on an additive scale between the effect of male sex and
338 HCV-infection ($S=0.71$).

339 The estimated increased odds for women in the HCV antibody^{+ve}
 340 cohort compared to those in the HCV antibody^{-ve} cohort further
 341 increased when only women were included in the data set who had tested
 342 RNA-positive (OR, 4.57). Increased odds were also calculated for those
 343 women who tested RNA-negative (OR, 2.89). For men, estimates for the
 344 effect of HCV-infection on the odds of having a diagnosis of T2DM
 345 were similar in the full data set (OR, 1.97), the RNA-positives (OR,
 346 2.07) or RNA-negatives (OR, 2.02). However, restricting the cohort to
 347 RNA-negatives, the variance for estimates increased and some of the
 348 differences in the odds between people in the HCV-positive cohort and
 349 the HCV antibody^{-ve} cohort were not statistically significant (Table 4).

350 **Hazard of T2DM diagnosis later than one year after HCV diagnosis**

351 In the HCV antibody^{-ve} cohort, increasing social deprivation was
 352 associated with an increased hazard of having a diagnosis of T2DM in
 353 the period later than one year after HCV diagnosis. However, in the
 354 HCV antibody^{+ve} cohort, increasing social deprivation was associated
 355 with a decreased hazard of having a diagnosis of T2DM (Table 5). The
 356 lowest hazard of having a diagnosis of T2DM was observed for the
 357 14,298 people in the HCV antibody^{+ve} cohort who lived in areas of

358 highest deprivation (1.4%) which was (non-significantly) lower than the
 359 hazard for the 34,470 members of the HCV antibody^{-ve} cohort living in
 360 the same areas of high deprivation (1.9%; HR, 0.88; 95% CI, 0.75-1.03
 361 $P=0.11$). The highest hazard was observed for the 2401 people in the
 362 HCV antibody^{+ve} cohort who lived in areas of lowest deprivation (2.5%)
 363 which was (significantly) higher than the hazard for the 10,957 members
 364 of the HCV antibody^{-ve} cohort living in the same areas of low
 365 deprivation (1.6%; HR, 1.53; 95% CI, 1.14-2.04 $P<0.01$). The synergy
 366 indices indicate negative interaction on an additive scale between the
 367 effect of deprivation and HCV-infection.

368 Slightly higher effects of HCV-infection on the hazard of being
 369 diagnosed with T2DM more than one year after HCV diagnosis were
 370 estimated when restricting the HCV-positive cohort to those who have
 371 tested RNA^{+ve} (indicative of chronic infection). Increased hazards were
 372 also estimated for those HCV antibody^{+ve} who tested RNA-negative and
 373 who lived in areas with high or low deprivation; however, due to the
 374 small sample size, those differences were not statistically significant
 375 (Table 5).

376 **Discussion**

377 This study compares the risk of receiving a diagnosis of T2DM in a
 378 cohort of all people who have been diagnosed HCV antibody^{+ve} in
 379 Scotland (the vast majority of whom will have acquired infection
 380 through injecting drug use) with that of a three times larger HCV
 381 antibody^{-ve} cohort matched on year of birth, sex and neighbourhood.
 382 The HCV antibody^{+ve} cohort was further stratified by RNA-status to
 383 check whether any additional risk attributed to HCV infection was
 384 related to the virus infection itself or to other factors related to the
 385 infection. Further the effect of HCV infection in three time periods -
 386 *pre*-HCV, *peri*-HCV and *post*-HCV diagnosis was studied to investigate
 387 any bias due to increased testing for T2DM at the time of HCV
 388 diagnosis.

389 This study shows that nationwide over a time-period of
 390 approximately 12 years there were approximately 14 additional cases of
 391 T2DM for every 10,000 HCV-infected people compared to what would
 392 have been observed in a HCV antibody^{-ve} cohort of identical size and
 393 characteristic. The excess risk was similarly low among RNA^{+ve} when
 394 taking into account the excess risk among RNA^{-ve}. Including those with
 395 HCV who are undiagnosed (nationwide approximately 50%, (25)), we

396 would expect that the total excess number of people with HCV-antibody
397 infection who have developed HCV-related T2DM up to this point in
398 time is less than 100.

399 While this is the first study to estimate the extra number of
400 HCV-related T2DM cases for a whole nation, increases in risk of those
401 with HCV have been reported elsewhere (1-4). For the national health
402 system of Scotland, compared to total number of people reported to have
403 been diagnosed with T2DM (265,000 between 2000 and 2012), the
404 increase of less than 100 cases in a 12-year period is relatively small.
405 Similarly, for the HCV-infected individual, compared to lifestyle
406 choices related to an increase in T2DM risk, the increase in risk related
407 to HCV-infection from 2.7% to 2.9% seems comparably low. The
408 relatively small difference in risk observed in our study indicates the
409 necessity to study the association between HCV-infection and T2DM in
410 large, well-defined study populations. Ruhl et al. (9) found no
411 association between HCV and either diabetes or insulin resistance (IR)
412 in their US population based study, involving 277 HCV antibody^{+ve}
413 individuals (compared to the 21,929 studied here); a relationship
414 between HCV and diabetes could only be found among those with
415 elevated enzyme activity. Ruhl et al. thus suggest that the previously
416 reported findings of a strong relationship with diabetes may have

417 resulted from the increased liver enzyme activity in the HCV
418 populations studied (9). Further, a recent meta-analysis has found an
419 association between the presence of IR and advanced fibrosis in those
420 with HCV genotype 1 (the most common genotype in the US), but not
421 for genotype 3 (27). We lacked data on liver enzyme activity, IR and
422 HCV genotype in this database linkage study to be able to investigate
423 this further in a larger cohort.

424 Matching allowed us to control for the effects of age, sex and
425 neighbourhood; the latter being a proxy for social deprivation and
426 regional differences in testing and recording for both conditions.
427 However, estimates of the number of additional cases of T2DM in those
428 with HCV-infection could have been biased from other risk factors for
429 T2DM for which information was not available. Ethnicity is known to be
430 related to T2DM, with people of South Asian background living in the
431 UK having 3-4 times higher risk of developing T2D during their life
432 compared to the majority white population (20). Moreover, people of
433 South Asian ethnicity are known to have a higher prevalence of HCV
434 (28), so a higher proportion of people with South Asian ethnicity would
435 be expected in the HCV-positive cohort. However, the South Asian
436 population in Scotland is very small ($\approx 1\%$ in the 2001 census), so that
437 confounding from a varying ethnic composition of the HCV-positive

cohort and the HCV-negative cohort can be expected to be small.
 Body-mass is a further known risk factor for T2DM, and it is possible
 that differences in BMI may confound the association between
 diagnoses of HCV and T2DM. However, since social deprivation and
 obesity are closely correlated in Scotland (14), matching by
 neighbourhood should have increased comparability of both cohorts, as
 indicated by similar proportions of people with a record of an obesity
 related hospitalization in the HCV antibody^{+ve} and the HCV antibody^{-ve}
 cohort. Similarly, alcohol consumption is a known risk factor for T2DM
 (29) and because alcohol consumption is positively related to
 HCV-status it could be expected that the proportion of people with high
 alcohol consumption was higher in the HCV-positive cohort compared
 to the HCV-negative cohort. Indeed, compared to people in the
 HCV-negative cohort, people in the HCV-positive cohort had a
 4.6-times higher risk of having an alcohol-related hospitalization. This
 bias from other risk factors related to T2DM might explain the
 observation in our study that compared to people in the HCV
 antibody^{-ve} cohort, people with resolved HCV-infection
 (RNA-negative) were still at higher risk of having a diagnosis of T2DM.
 The study also shows that the effect of diagnosed HCV-infection on
 the relative proportions of people with a diagnosis of T2DM was time

459 dependent. Partitioning of the risk period clearly showed that the
460 increased risk is mainly due to increased T2DM diagnosis around the
461 time of HCV diagnosis, while the 10% increased risk more than one year
462 *prior* to HCV diagnosis and one year *post* HCV diagnosis were
463 considerably lower than the estimate from the meta-analyses.
464 Interestingly, the estimate of a 10% increased relative risk is very similar
465 to that from the largest cohort study that had been included in the
466 meta-analyses (30) although the estimate of absolute T2DM prevalence
467 in the HCV antibody^{-ve} cohort in our study (3.2%) was much lower than
468 that in the US study (13%) or indeed any other cohort study but one
469 included in the meta-analyses. Increased T2DM within ± 1 year is likely
470 related to ascertainment bias. However, neither guidelines by the
471 Scottish Intercollegiate Guideline Network (SIGN guidelines 116) nor
472 by the National Institute of Clinical Excellence recommend testing for
473 HCV infection in people diagnosed with T2DM and guidelines by the
474 European Association for the Study of the Liver only recommend testing
475 for T2DM *prior* to treatment for HCV infection, since ‘poorly controlled
476 diabetes’ is a contra-indication for treatment with interferon containing
477 regimens. Therefore, the most likely reason for the increased T2DM
478 diagnosis *peri*-HCV diagnosis is related to people showing clinical
479 symptoms indicative of liver disease. It seems likely that for people with

480 signs of liver disease, a blood sample for glucose testing is collected at
481 the same time as samples for HCV tests and liver function
482 measurements. We do not have access to laboratory test databases in
483 order to investigate the potential for ascertainment bias further. While
484 there was a highly significant correlation between increasing age and the
485 risk of T2DM diagnosis, there was no significant increase with age in the
486 effect of HCV infection on the risk of T2DM ($P=0.34$ for inclusion of an
487 HCV*age interaction term). This result indicates that the observed effect
488 of HCV infection on the risk of T2DM is more likely caused by other
489 factors related to HCV infection than by the (slowly progressing) action
490 of the virus. However, our HCV infected cohort is still relatively young
491 (median age at HCV diagnosis was 33 years) and has been followed up
492 for a relatively short time (median of 6.4 years), thus the excess risk of
493 T2DM may still change as our cohort advances in age and duration of
494 infection.

495 Male sex and living in areas of highest deprivation decreased effects
496 of HCV infection on the risk of T2DM diagnosis. This effect
497 modification was not related to follow-up time, age at HCV-infection or
498 RNA-status since those did not differ within sex and social deprivation.
499 Since male sex and high deprivation are positively related to T2DM risk,
500 our observation does not confirm the suggestion from (11) that relative

501 effects of HCV on T2DM risk are higher in people at increased risk of
502 T2DM. However, the effect modification could be explained by
503 different uptake of health care (and thereby testing for diabetes) in men
504 living in areas of high deprivation. The effect modification could explain
505 some of the heterogeneity that both meta analyses found, since few of
506 the reviewed studies stratified by sex and none by social deprivation.
507 However, widely accepted biological models of the effects of HCV
508 infection on T2DM risk (5-7) do not explain the observed effect
509 modification. Moreover, while sex, social deprivation and year of birth
510 were included in our matched analysis to increase efficiency of the study
511 (31), the analysis of effect modification by sex, social deprivation, year
512 and age was purely exploratory.

513 Ideally, every person in the HCV-positive cohort should have been
514 followed-up from the date of HCV-infection to development of T2DM
515 or censoring. However, because date of HCV-infection was unknown,
516 the follow-up period and thereby the risk of T2DM diagnosis *pre*-HCV
517 diagnosis was heterogeneous. Additionally, the T2DM database is only
518 approximately complete from 2004 onwards, with regional differences
519 in the date from which diagnoses of T2DM were reported to the
520 database. By matching people in the HCV antibody^{-ve} cohort to those in
521 the HCV antibody^{+ve} cohort by year of birth and place of residence and

522 by adequately controlling for the effect of matching in the analysis we
523 managed to reduce the potential bias for the odds ratio from
524 heterogeneous follow-up times. However, the estimated odds of T2DM
525 diagnosis *pre*-HCV diagnosis in both cohorts are difficult to interpret. In
526 addition, since date of HCV-infection and date of onset of T2DM both
527 were unknown to us, the temporal relationship of onset of HCV infection
528 and T2DM is not known. Indeed, T2DM has been described as a risk
529 factor for contracting HCV (12). However, an estimated 86% of
530 HCV-infection in Scotland is related to injecting drug use (32) and a
531 large fraction of those diagnosed HCV-positive will have been infected
532 in their early drug using career. Given that the risk of developing T2DM
533 increases with age, it is unlikely that the increased risk for HCV in those
534 with T2DM was responsible for the results of our study.

535 Our study has demonstrated that on the population level the size of
536 the effect of HCV antibody status on T2DM is smaller than effects of
537 many life style choices (e.g., obesity, smoking and alcohol consumption)
538 and therefore not as significant a public health concern as previously
539 suggested from predominantly clinic based studies. Findings were
540 similarly observed for both RNA^{+ves} (chronic) and RNA^{-ves} (resolved)
541 which further indicates that the observed differences in risk of T2DM
542 diagnosis were not related to the virus itself but to factors related to the

543 infection (e.g., factors related to drug abuse). However, given the
544 increased risk for HCV-related disease progression in those affected by
545 both conditions (33), further research is required to identify whether
546 screening and earlier treatment for T2DM improves outcomes among
547 people with a diagnosis of chronic HCV. Socio-economic status, sex and
548 a history of alcohol use and injecting drug use modify the effect of HCV
549 on T2DM which could explain some of the discrepancies between
550 different studies given the different patterns of these factors in different
551 populations.

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561

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Table 1: Characteristics of the study population

Variable	Level	HCV Ab ^{+ve} cohort (N)	HCV Ab ^{-ve} cohort (N)	%	% Complete Matches ¹
Sex	Women	7067	20,956	32	97
	Men	14,862	44,118	68	97
Year of birth	<1950	1335	3859	6	90
	1950-1959	2876	8521	13	96
	1960-1969	7246	21,545	33	97
	1970-1979	7616	22,656	35	98
	≥1980	2856	8493	13	97
Year of diagnosis	<2000	6592	19526	30	96
	≥2000	15,337	45,548	70	97
Deprivation	Low	2824	13,604	13/21 ³	96
	Medium	2678	9628	12/15 ³	96
	High	16,427	41,842	75/64 ³	97
Alcohol-related hospitalization ²	Yes	4812	2942	22/4.5 ³	
Obesity-related hospitalization ²	Yes	60	209	0.3/0.3 ³	
<i>Total</i>		21,929	65,074		97

¹ A complete match is 1 person in the HCV antibody^{+ve} cohort and 3 people in the HCV antibody^{-ve} cohort matched on year of birth, sex and postcode sector of residence.

² Alcohol and obesity related hospitalization prior to HCV diagnosis; ICD9 codes and ICD10 codes as listed in patients and methods.

³ HCV antibody^{+ve} and HCV antibody^{-ve}, respectively.

681 Table 2: Number (and proportion) of people with T2DM in the HCV antibody^{+ve}
 682 cohort (including for those PCR^{+ve} and PCR^{-ve}) and in the HCV antibody^{-ve} cohort
 683 according to time since HCV diagnosis.

Period since HCV diagnosis ¹	HCV Ab ^{-ve} (N=65,074)		HCV Ab ^{+ve} (N=21,929)		HCV Ab ^{+ve} & PCR ^{+ve} (N=15,827)		HCV Ab ^{+ve} & PCR ^{-ve} (N=3,927)	
	Diabetes ^{+ve}	%	Diabetes ^{+ve}	%	Diabetes ^{+ve}	%	Diabetes ^{+ve}	%
>1 year pre	524	0.81	187	0.85	157	0.99	23	0.59
± 1 year	184	0.28	141	0.64	115	0.73	18	0.46
>1 year post	1064	1.64	300	1.37	234	1.48	49	1.25
<i>Total</i>	1772	2.72	628	2.86	506	3.20	90	2.29

684 ¹ For those in the HCV antibody^{-ve} cohort, HCV diagnosis data was taken to be the
 685 same as their respective HCV antibody^{+ve} cohort members, for the purpose of analysis.

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691 Table 3: Odds of having been diagnosed with T2DM in the period up to 1 year before
 692 HCV diagnosis in the HCV antibody^{+ve} cohort (total and broken down by PCR status)
 693 compared to the HCV antibody^{-ve} cohort^{1,2}

694

Sex	Deprivation	Diabetes ^{+ve} /HCV Ab ^{-ve}	Diabetes ^{+ve} /HCV Ab ^{+ve}	aOR ³ (95% CI; <i>P</i>)	S ⁴
Antibody ^{+ve}					
F	Low	17/4345 (0.4%)	23/941 (2.4%)	4.02 (2.32-6.96); <i>P</i> <0.01	
F	Medium	16/3036 (0.5%)	10/830 (1.2%)	1.92 (0.95-3.86); <i>P</i> =0.08	0.42
F	High	101/13,575 (0.7%)	38/5296 (0.7%)	1.05 (0.66-1.69); <i>P</i> =1.00	0.32
M	Low	77/9259 (0.8%)	40/1883 (2.1%)	2.33 (1.42-3.83); <i>P</i> <0.01	0.62
M	Medium	57/6592 (0.9%)	19/1848 (1.0%)	1.11 (0.58-2.11); <i>P</i> =0.99	0.28
M	High	256/28,267 (0.9%)	57/11,131 (0.5%)	0.61 (0.43-0.87); <i>P</i> <0.01	0.15
Antibody ^{+ve} and PCR ^{+ve}					
F	Low	12/3067 (0.4%)	18/661 (2.7%)	4.35 (2.33-8.13); <i>P</i> <0.01	
F	Medium	10/2117 (0.5%)	7/575 (1.2%)	2.05 (0.93-4.50); <i>P</i> =0.09	0.42
F	High	80/9098 (0.9%)	33/3576 (0.9%)	1.14 (0.67-1.93); <i>P</i> =0.96	0.35
M	Low	59/6886 (0.9%)	34/1375 (2.5%)	2.61 (1.50-4.55); <i>P</i> <0.01	0.63
M	Medium	44/4877 (0.9%)	16/1360 (1.2%)	1.23 (0.60-2.54); <i>P</i> =0.93	0.30
M	High	202/20,936 (1.0%)	49/8280 (0.6%)	0.68 (0.46-1.01); <i>P</i> =0.06	0.19
Antibody ^{+ve} and PCR ^{-ve}					
F	Low	0/841 (0.0%)	4/169 (2.4%)	6.14 (1.38-27.21); <i>P</i> <0.01	
F	Medium	4/669 (0.6%)	3/175 (1.7%)	2.69 (0.55-13.23); <i>P</i> =0.42	0.63
F	High	18/3343 (0.5%)	4/1294 (0.3%)	0.74 (0.21-2.61); <i>P</i> =0.96	0.09
M	Low	11/1339 (0.8%)	5/267 (1.9%)	2.45 (0.63-9.55); <i>P</i> =0.36	0.54
M	Medium	9/1010 (0.9%)	3/283 (1.1%)	1.07 (0.25-4.66); <i>P</i> =1.00	0.32
M	High	33/4450 (0.7%)	4/1739 (0.2%)	0.29 (0.09-0.98); <i>P</i> =0.04	0.01

695 ¹For those in the HCV antibody^{-ve} cohort, HCV diagnosis date was taken to be the
 696 same as their respective HCV antibody^{+ve} cohort members, for the purpose of
 697 analysis.

698 ²Based on the likelihood-ratio test comparing the antibody^{+ve} cohort to the
 699 antibody^{-ve} cohort, interaction-terms other than sex × HCV and deprivation ×
 700 HCV were deemed not statistically significant and therefore excluded from the
 701 final model.

702 ³Adjusted OR and *P* for exposure to HCV-infection within strata of sex and social
 703 deprivation. Odds ratios adjusted for age at HCV diagnosis, year of HCV
 704 diagnosis and the extra correlation due to the matching.

705 ⁴Synergy Index.

706

Table 4: Odds of having a diagnosis of T2DM in the period within ± 1 year of the time of HCV diagnosis in the HCV antibody^{+ve} cohort (total and broken down by PCR status) compared to the HCV antibody^{-ve} cohort^{1,2}

Sex	Diabetes ^{+ve} /HCV Ab ^{-ve}	Diabetes ^{+ve} /HCV Ab ^{+ve}	aOR ³ (95% CI; <i>P</i>)	S ⁴
Antibody ^{+ve}				
F	36/20,626 (0.2%)	46/6996 (0.7%)	3.78 (2.29-6.25); <i>P</i> <0.01	
M	142/43,406 (0.3%)	95/14,746 (0.6%)	1.97 (1.46-2.65); <i>P</i> <0.01	0.71
Antibody ^{+ve} and PCR ^{+ve}				
F	25/13,230 (0.2%)	38/4486 (0.8%)	4.57 (2.56-8.18); <i>P</i> <0.01	
M	111/30,223 (0.4%)	77/10,273 (0.7%)	2.07 (1.48-2.90); <i>P</i> <0.01	0.66
Antibody ^{+ve} and PCR ^{-ve}				
F	6/4591 (0.1%)	6/1555 (0.4%)	2.89 (0.52-16.01); <i>P</i> =0.31	
M	18/6283 (0.3%)	12/2131 (0.6%)	2.02 (0.67-6.10); <i>P</i> =0.29	1.01

¹For those in the HCV antibody^{-ve} cohort, HCV diagnosis date was taken to be the same as their respective HCV antibody^{+ve} cohort members, for the purpose of analysis.

²Based on the likelihood-ratio test comparing the antibody^{+ve} cohort to the antibody^{-ve} cohort, interaction-terms other than sex $\times$ HCV were deemed not statistically significant and therefore excluded from the final model.

³Adjusted OR and *P* for exposure to HCV-infection within strata of sex. Odds ratios adjusted for age at HCV diagnosis, year of HCV diagnosis, social deprivation and the extra correlation due to the matching.

⁴Synergy Index.

Table 5: Hazard of being diagnosed with T2DM in the period >1 year after the time of HCV diagnosis in the HCV antibody^{+ve} cohort (total and broken down by PCR status) compared to the HCV antibody^{-ve} cohort^{1,2}

Deprivation	Diabetes ^{+ve} /HCV Ab ^{-ve}	Diabetes ^{+ve} /HCV Ab ^{+ve}	aHR ³ (95% CI; <i>P</i>)	S ⁴
Antibody ^{+ve}				
Low	175/10,957 (1.6%)	61/2401 (2.5%)	1.53 (1.14-2.04); <i>P</i> <0.01	
Medium	137/7740 (1.8%)	43/2308 (1.9%)	1.14 (0.81-1.60); <i>P</i> =0.47	0.74
High	646/34,470 (1.9%)	196/14,298 (1.4%)	0.88 (0.75-1.03); <i>P</i> =0.11	0.36
Antibody ^{+ve} and PCR ^{+ve}				
Low	118/8158 (1.4%)	47/1750 (2.7%)	1.71 (1.21-2.40); <i>P</i> <0.01	
Medium	100/5659 (1.8%)	35/1677 (2.1%)	1.26 (0.86-1.86); <i>P</i> =0.24	0.70
High	470/25,027 (1.9%)	152/10,448 (1.5%)	0.89 (0.74-1.07); <i>P</i> =0.22	0.39
Antibody ^{+ve} and PCR ^{-ve}				
Low	25/1459 (1.7%)	9/376 (2.4%)	1.46 (0.68-3.13); <i>P</i> =0.33	
Medium	19/1395 (1.4%)	4/401 (1.0%)	0.70 (0.24-2.05); <i>P</i> =0.51	(-) ⁵
High	91/6489 (1.4%)	36/2657 (1.4%)	1.10 (0.75-1.62); <i>P</i> =0.62	0.53

¹For those in the HCV antibody^{-ve} cohort, HCV diagnosis date was taken to be the same as their respective HCV antibody^{+ve} cohort members, for the purpose of analysis.

²Based on the likelihood-ratio test comparing the antibody^{+ve} cohort to the antibody^{-ve} cohort, interaction-terms other than deprivation × HCV were deemed not statistically significant and therefore excluded from the final model.

³Adjusted HR and *P* for exposure to HCV-infection within strata of social deprivation. Odds ratios adjusted for age at HCV diagnosis, sex, year of HCV diagnosis and the extra correlation due to the matching.

⁴Synergy Index.

⁵To ease comparison between different models, the reference category (antibody^{-ve} and low deprivation) was fixed between models. This caused a negative (invalid) synergy index.

720 Figure 1: Flowchart describing inclusion (boxes in the left column) and
721 exclusion criteria (boxes in the right column) for the HCV+ve cohort