

1 **The role of metformin and statins in the incidence of epithelial ovarian cancer in type 2 diabetes: a**
2 **cohort and nested case-control study.** (Final draft)

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21

22 Running title: Metformin and statins and the incidence of ovarian cancer

23

24 **Abstract**

25

26 Objective. To obtain evidence of the effects of metformin and statins on the incidence of ovarian cancer in
27 women with type 2 diabetes (T2D).

28 Design. A retrospective cohort study and nested case-control study.

29 Setting. The data were obtained from a diabetes database (FinDM) combining information from several
30 nationwide registers.

31 Population. A cohort of 137 643 women over 40 years old and diagnosed with T2D during 1996 through
32 2011 in Finland.

33 Methods. In full cohort analysis Poisson regression was utilized to estimate the hazard ratios (HR) in
34 relation to ever use of metformin, insulin, other oral antidiabetic medication or statins. In the nested case-
35 control analysis 20 controls were matched to each case of ovarian cancer. Conditional logistic regression
36 was used to estimate HRs in relation to medication use and cumulative use of different medications. The
37 estimates were adjusted for age and duration of T2D.

38 Main outcome measure. Incidence of ovarian cancer

39 Results. 303 women were diagnosed with ovarian cancer during the follow-up. Compared with other forms
40 of oral antidiabetic medication, metformin (HR 1.02, 95 % CI 0.72–1.45) was not found to be associated
41 with the incidence of ovarian cancer. Neither was there evidence for statins to affect the incidence (HR
42 0.99, 95 % CI 0.78–1.25). In nested case-control analysis the results were essentially similar.

43 Conclusions. No evidence of an association between the use of metformin or statins and the incidence of
44 ovarian cancer in patients with T2D was found.

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47 Keywords. Metformin, statins, ovarian cancer, cancer incidence, cohort study, case-control study

48 Tweetable abstract. No evidence found for metformin or statins reducing the incidence of ovarian cancer.

49

50

51 **Introduction**

52

53 Ovarian cancer accounts for 3.7 % of all cancers in women worldwide but it is one of the most lethal
54 cancers, causing 140,000 deaths annually(1). The risk factors of ovarian cancer include genetic factors
55 (BRCA1, BRCA2, HNPCC), nulliparity, endometriosis, pelvic inflammatory disease, postmenopausal hormone
56 therapy and polycystic ovary syndrome (PCOS)(2,3). A recent meta-analysis also showed that increasing
57 body weight in premenopausal women is associated with an increased incidence of ovarian cancer(4).
58 Protective factors include multiparity, lactation, oral contraceptives, hysterectomy, salpingectomy and
59 sterilization(2,3).

60 People with type 2 diabetes (T2D) have been reported to have an increased incidence of various cancers,
61 including ovarian cancer, compared with those without diabetes, the risk being highest in insulin-treated
62 patients(5). However, Weiderpass *et al.* did not find any association between diabetes and ovarian
63 cancer(6). Metformin is an oral antidiabetic medication which is recommended as the first-line treatment in
64 T2D(7). Metformin has anti-mitotic, anti-angiogenic and anti-inflammatory properties(8). The main
65 signalling route of metformin is via AMP-activated protein kinase (AMPK)(9,10). In some epidemiological
66 studies the use of metformin has been linked to lower incidence of several cancer types(11,12). Evans *et al.*
67 reported a 23% decrease in the incidence of any type of cancer in those using metformin compared with
68 those on other antidiabetic medication(13). In another study a reduction of ovarian cancer incidence in
69 women with diabetes on metformin treatment was reported(14). However, there are also publications

70 where no association between in the incidence of ovarian cancer and the use of metformin has been
71 found(15,16).

72

73 Persons with T2D have an increased risk of cardiovascular diseases and hypercholesterolaemia, which are
74 widely treated with statins. For example, in Finland, 79 % of newly diagnosed people with T2D use statins
75 for secondary and 40 % for primary prevention of coronary heart disease(17). Statins (HMG-CoA reductase
76 inhibitors) block formation of cholesterol by inhibiting HMG-COA conversion to mevalonate(18). The
77 possible cancer-preventing effect of statins is thought to be mediated partly by this mechanism(18).

78 In the present register-based retrospective cohort study and case-control analysis we assessed the role of
79 antidiabetic medication and statin use on the incidence of epithelial ovarian cancer in women with T2D.

80

81 **Methods**

82

83 The STROBE guidelines for reporting of observational studies were followed in this article(19) .

84

85 **Data sources**

86 The data were obtained from the FinDM database, in which information from several Finnish nationwide
87 registers and register-holders (National Institute for Health and Welfare, Statistics Finland, the Care
88 Register for Health Care and the Social Insurance Institution) has been combined from 1964 to 2011(20).

89 The FinDM database includes accurate information about the quantity and the date of purchase of all
90 medication prescribed by doctors and reimbursed by the Social Insurance Institution, including antidiabetic
91 and statin medication, starting from 1994. Data on diagnoses from hospital records were obtainable from
92 1969 for inpatients and from 1998 for outpatients. Information on surgical procedures performed in

93 hospitals is available from 1987. Identification of persons with diabetes are entered in the register on the
94 basis of diagnoses documented in hospital records or by reimbursement for antidiabetic medication.
95 Comparison of data from FinDM against a regional diabetes register covering the Helsinki district has shown
96 good agreement(21). In certain cases, the duration of T2D is likely to have been longer than indicated from
97 the register, as FinDM does not carry information on former treatment of diet-controlled diabetes which
98 occurred only in an outpatient primary-care setting. The categorization of patients in the register in to type
99 1 (primary insulin-dependent diabetes mellitus) and type 2 diabetes was based primarily on the antidiabetic
100 medication used as first-line treatment.

101 The records in FinDM are linked to information from the Finnish Cancer Registry, which has outstanding
102 coverage of over 99% of all cancer cases in Finland since 1953(22). The date of diagnosis, histology and
103 morphology of cancer are recorded in the Finnish Cancer Registry. Information about the date of the death
104 were available from Statistics Finland. Data linkage between various registers was carried out on the basis
105 of personal identification codes unique to each resident of Finland.

106

107 Identification of the study cohort

108 Details of the cohort selection process are presented in a flow chart (Figure 1). From our source population
109 contained in the FinDM database we first identified 172 070 women with incident T2D diagnosed between
110 1 January 1996 and 31 December 2011. With this inclusion criterion the data covering the whole purchase
111 history of the drugs under study from the diagnosis of T2D onwards up to the end of 2011 was available for
112 all women of our intended study cohort.

113 The entry to the follow-up for the incidence of ovarian cancer was set either at the date of 40th birthday, or
114 at the date when one year had passed after the diagnosis of T2D, whichever date occurred later. Exclusion
115 of the first year from the follow-up was done in order to reduce the risk of detection bias and reverse
116 causality bias associated with the increased surveillance for cancer immediately after diagnosis of diabetes
117 (5). Women with a diagnosis of ovarian cancer before cohort entry were excluded. In addition, women with

118 certain prior gynaecological operations, including oophorectomy, salpingo-oophorectomy or hysterectomy
119 with bilateral salpingo-oophorectomy, before entry were excluded from the cohort. Data on surgical
120 operations were available only from 1987 onwards, leaving the possibility of some women with prior
121 operations remaining in the cohort. This concerned mainly women in the older age categories. The final
122 cohort consisted of 137 643 women diagnosed with T2D between 1996 and 2011.

123 In addition, a nested case-control study within the cohort was conducted mainly in order to evaluate the
124 association of ovarian cancer with the cumulative use of the medications under study. This design,
125 compared to a full cohort design, enables more straightforward calculation of the number of defined daily
126 doses (DDD) of medication used by each patient prior to their respective index date for analysing the effect
127 of the accumulated DDD. For each case, up to 20 controls were selected without replacement from among
128 those women in the cohort who were alive and at risk of ovarian cancer at the date of ovarian cancer
129 diagnosis of the case, and who were also matched for both age (date of birth) and duration of diabetes (\pm
130 182 days).

131

132 Classification of medication

133 Exposure to antidiabetic medication was evaluated in three separate categories: metformin, other oral
134 antidiabetic medication and insulin. The use of statins was assessed as one category. Exposure to any
135 medication was considered to begin 365 days after its first purchase date to avoid reverse causality
136 problem and to allow a minimum reasonable latency period for any medication effect. In both the full-
137 cohort analysis and the nested case-control analysis patients were categorized as being exposed to a given
138 medication from this moment onwards throughout the individual follow-up time (ever- vs. never-exposed).
139 In addition, the effects of cumulative use of metformin, insulin, other forms of oral antidiabetic medication
140 and statins were assessed in the nested case-control analysis using the total amount of defined daily doses
141 (DDDs) purchased during the follow-up period.

142

143 Follow-up

144 Follow-up of each patient started one year after diagnosis of T2D or at the age of 40 whichever happened
145 later, and it ended on the date of diagnosis of ovarian cancer, oophorectomy for reasons other than cancer,
146 death or the end of the study period (31 December 2011), whichever occurred earliest.

147

148 Statistical analysis

149 In the full-cohort analysis, a multiple Poisson regression model(23) was used to estimate the hazard ratios
150 (HRs) with 95 % confidence intervals (95% CIs) of the incidence of ovarian cancer in relation to ever use of
151 metformin, other forms of antidiabetic medication and statins. In this model, the effects of current age and
152 duration of T2D were assumed to obey a piecewise constant hazards pattern over chosen intervals of these
153 two time scales. Age was split into 5-year intervals from 40-44 years to 85-89 years plus one more interval
154 covering 90-106 years, and duration of T2D into intervals that are shown in Table 1. In the nested case-
155 control analysis, the corresponding hazard ratios with 95 % CIs were estimated by means of conditional
156 logistic regression (24) in relation to the ever use of different forms of antidiabetic medication and statins.
157 Cumulative doses were categorized according to tertiles of total amounts of DDDs used. The register data
158 were preprocessed using SAS/STAT® software version 9.4 of the SAS System for Windows, with consecutive
159 data transformations and the statistical analysis performed in R environment version 3.3.2 (25). A person-
160 period file was created using the Lexis tools in the Epi package of R, where individual follow-up time of each
161 person was simultaneously split into the appropriate periods of age, duration of T2D and the time-
162 dependent medication use status(26,27). In the analysis of the full cohort data, the Poisson regression
163 model was fitted using the glm function(25), and in the analysis of the nested case-control data the
164 conditional logistic regression model was fitted using the clogit function from the survival package of R(28).

165

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169

170 **Results**

171 The total follow-up covered 748 282 person-years at risk (Table 1), the mean follow-up time being 5.4
172 years. During the study period, 303 women were diagnosed with epithelial ovarian cancer. The incidence of
173 ovarian cancer was highest in the age-group of 60–69 years (51.4 per 100 000 person–years) and in the
174 group where the duration of diabetes was 5–8 years (52.5 per 100 000 person–years).

175 In the nested case-control analysis, we selected 6060 matched (on age and T2D duration) controls for the
176 303 women diagnosed with epithelial ovarian cancer. Two thirds of the cases and controls were ever-users
177 of metformin, and over 50% were ever-users of statins (Table 1). The most used other oral antidiabetic
178 medication were sulphonylureas and the most used statin was simvastatin. Details on ATC codes and
179 percentages of other oral antidiabetic medication used, and statins, are listed in Table S1.

180 In the full cohort–analysis, neither ever use of metformin, nor ever use of insulin were found to be
181 associated with a different incidence of ovarian cancer, when compared with ever use of other oral
182 antidiabetic medication (Table 2); the adjusted HR with ever use of metformin was 1.02 (95 % CI 0.72–1.45)
183 and that for ever use of insulin was 1.19 (95% CI 0.73–1.93). The incidence of ovarian cancer was not found
184 to be different with ever use of statins either with a HR 0.99, 95% CI 0.78–1.25). No consistent trend was
185 observed for the incidence of ovarian cancer by time since onset of T2D (Figure S1), nor was there sufficient
186 evidence for any interaction between duration of T2D and any of the medications concerned (data not
187 shown).

188 In the case-control analysis, the main findings were similar. Ever use of metformin had an adjusted HR of
189 0.91 (95% CI 0.61–1.34) and ever use of insulin an adjusted HR of 1.19 (95% CI 0.72–1.97) when compared
190 with ever use of other oral antidiabetic medication. The incidence of ovarian cancer was not found to be

191 associated with ever use of statins either, the adjusted HR being 0.96 (95% CI 0.75–1.23). There was no
192 evidence of any interaction effect of ever use of statins and metformin, the interaction hazard ratio being
193 0.88 (95% CI 0.54–1.45). Neither was any consistent trend observed in the incidence of ovarian cancer with
194 respect to rising cumulative use of metformin, other oral antidiabetic medication, insulin or statins in terms
195 of defined daily doses (Figure 2).

196

197 **Discussion**

198

199 Main findings

200 We found no evidence of an association between metformin or other forms of oral antidiabetic medication
201 and the incidence of epithelial ovarian cancer in 40 years or older women with T2D. Neither did we observe
202 any trend in the incidence of ovarian cancer with increasing defined daily doses of metformin. We **could**
203 not find any association between statin use and the risk of epithelial ovarian cancer either

204

205 Strengths and limitations

206 As far as we know, our study is the first in which the effect of statin use in patients with T2D and their risk
207 of ovarian cancer has been explored. Many of the previous studies on the risk of ovarian cancer in
208 association with medication have suffered from methodological issues and their sizes have been relatively
209 small.

210 A major strength of our study is the use of very reliable and comprehensive national registers. Patient's
211 details are entered into the diabetes register at the time of the first purchase for any form of antidiabetic
212 medication. Data in the register concerning the diagnosis date of T2D are considered to be fairly accurate.
213 The coverage of the prescription register of the Social Insurance Institution of Finland of reimbursed

214 medications prescribed by physicians is virtually complete for the pertinent study period(29). We also have
215 a reliable history of prior operations among the patients in the cohort. The other major strength of our
216 study lies in its time-dependent design. We are able to calculate the time-related use and to make good
217 estimates of cumulative amounts (DDDs) of metformin and other types of antidiabetic medication and
218 statins. However, defined daily doses of antidiabetic medication also correlate with the duration and
219 severity of type 2 diabetes.

220 Limitations of our study include the lack of information on the family history of ovarian cancer, and parity
221 of the women in the diabetes cohort. In addition, we do not have data on the BMI or other markers of
222 insulin resistance of the patients. However, the proportion of premenopausal women, in which obesity
223 would affect the incidence of ovarian cancer(4), is relatively small among women with T2D. Our study
224 cohort was confined to women who were at least 40 years old. This restriction should not carry any
225 essential implications to the overall picture conveyed by our results, considering that the contribution of
226 younger women to the total caseload of ovarian cancer is very modest also in the population of women
227 with T2D. In fact, no cases of ovarian cancer were found among women in the FinDM population, who
228 fulfilled all the other inclusion criteria but who were less than 40 years old. Thus, the results of both the full
229 cohort analysis and the nested case-control analysis would remain the same whether this age restriction
230 was employed or not.

231 As to the measurement and classification of drug use we note that the national prescription register
232 contains only prescribed medications (for example, antidiabetic medications and statins) reimbursed by the
233 national health insurance system. Over-the-counter drugs and drugs dispensed in hospitals and outpatient
234 clinics are not covered by this register(29), but only a small proportion of persons with type 2 diabetes are
235 treated in health care facilities. Moreover, no direct data exist on whether the purchased drug was actually
236 taken or not. However, the concordance between self-reported medication use and information contained
237 in the prescription register has been shown to be quite good(30). In addition, exposure classification based
238 on registered purchases of diabetes drugs and statins before diagnosis of ovarian cancer is in no way

239 dependent on whether a study subject develops cancer or not. Therefore, any misclassification is most
240 likely nondifferential, which implies that the direction of a possible bias associated with it would be
241 “towards zero”, i.e. the estimated hazard ratios would have a tendency to be closer to 1 than the true HR.

242

243 Interpretation

244 The possible cancer-preventing effect of metformin has led to a considerable number of observational
245 studies in this field, although, many studies have had methodological challenges, for example time-related
246 biases, as a result of their observational nature(31). However, only a few studies have been published on
247 metformin and the incidence of ovarian cancer. In a systematic review by Dilokthornsakul *et al.*, little
248 evidence was found concerning the association between metformin use and the incidence of ovarian
249 cancer(16). In a retrospective cohort study, Tseng reported that women with type 2 diabetes who used
250 metformin had a decreased risk of ovarian cancer compared with those who did not use it(14). However,
251 the relatively large epidemiological case-control study carried out by Bodmer *et al.* did not find any
252 association between metformin use and a reduction of in the incidence of ovarian cancer(15). On the other
253 hand, long-term use of insulin was associated with an increased incidence of ovarian cancer(15). BMI
254 seemed not to have any effect on the incidence of ovarian cancer in their study.

255 In our study, the most used statin was simvastatin, which is categorized as a lipophilic statin. Hydrophilic
256 and lipophilic statins might have different impacts on cancer risk. In one study, lipophilic statins reduced
257 the risk of breast cancer(32). Both *in vitro* and *in vivo* studies have shown that lipophilic statins, at least,
258 have antiproliferative, pro-apoptotic, anti-invasive and radiosensitizing effects(33). In 2014 Liu *et al.*
259 published a review on statins and gynaecological cancers in which ovarian cancer incidence seemed to be
260 lower among statin users, and the protective effect was dose-dependent(34). There was no significant
261 benefit of statin use as regards other gynaecological cancers(34). However, in line with our findings, in
262 some other studies no association between statin use and the risk of ovarian cancer has been found(35-37).

263

264 **Conclusion**

265 We found no evidence for an association between the use of metformin or other forms of oral antidiabetic
266 medication and the incidence of epithelial ovarian cancer in women with T2D. Neither did we find any
267 evidence for an association between statin use and the risk of epithelial ovarian cancer.

268

269 Disclosure of interests

270 There are no conflicts of interest to disclose.

271

272 Contribution to authorship

273 EU, UP and MH drafted the article. MM, AH and EL had access to the databases and MM undertook the
274 analyses. EU, UP, MH, MM, AH, EL, MA, RS, PI-P, RA and JK reviewed the drafts.

275

276 Details of ethics approval

277 FinDM has received approval from the Ethics Committee of National Public Health Institute (the 30th of
278 January 2014, proceeding \$609). Data on individual persons in FinDM is stored according to Finnish data-
279 protection legislation. The data received by the research group were anonymized such that the personal
280 identity codes were converted into unidentified codes.

281

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285

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289

290 **Supporting Information**

291 Table S1. ATC codes and percentages of other forms of oral antidiabetic medication and statins.

292 Figure S1. Estimated hazard ratios (bullets) with 95% confidence intervals (segments about the bullets) for
293 ovarian cancer associated with different intervals of duration of T2D based on Poisson regression fitted on
294 full cohort data.

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388 Figure 1. Flow chart. Forming the cohort.

389

390 Table 1. Incidence rates of ovarian cancer (per 100,000 person-years), distribution of person-years at risk,
391 and numbers (%) of cases and matched controls by age, duration of diabetes and medication use. Cases
392 and controls were matched for age (± 182 days) and duration of diabetes (± 182 days).

393

394 Table 2. Adjusted estimates of hazard ratios (HR, with 95 % confidence intervals, CI) for the association
395 between ovarian cancer incidence and "ever use" of metformin and insulin compared with the use of other
396 forms of oral antidiabetic medication, and the use (at any time) of statins compared with no use of statins
397 at any time. The estimates are based on Poisson regression using the full-cohort data, and conditional
398 logistic regression using the nested case-control data, both adjusted for age and duration of diabetes.

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400 Figure 2. Estimated hazard ratios (with 95% confidence intervals) of ovarian cancer by cumulative doses of
401 different forms of antidiabetic medication and statins, adjusted for age and duration of diabetes
402 medication, using case-control data.

403

404 Table S1. ATC codes and percentages of other forms of oral antidiabetic medication and statins.

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406 Figure S1. Estimated hazard ratios (bullets) with 95% confidence intervals (segments about the bullets) for
407 ovarian cancer associated with different intervals of duration of T2D based on Poisson regression fitted on
408 full cohort data.

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Figure 1. Flowchart.

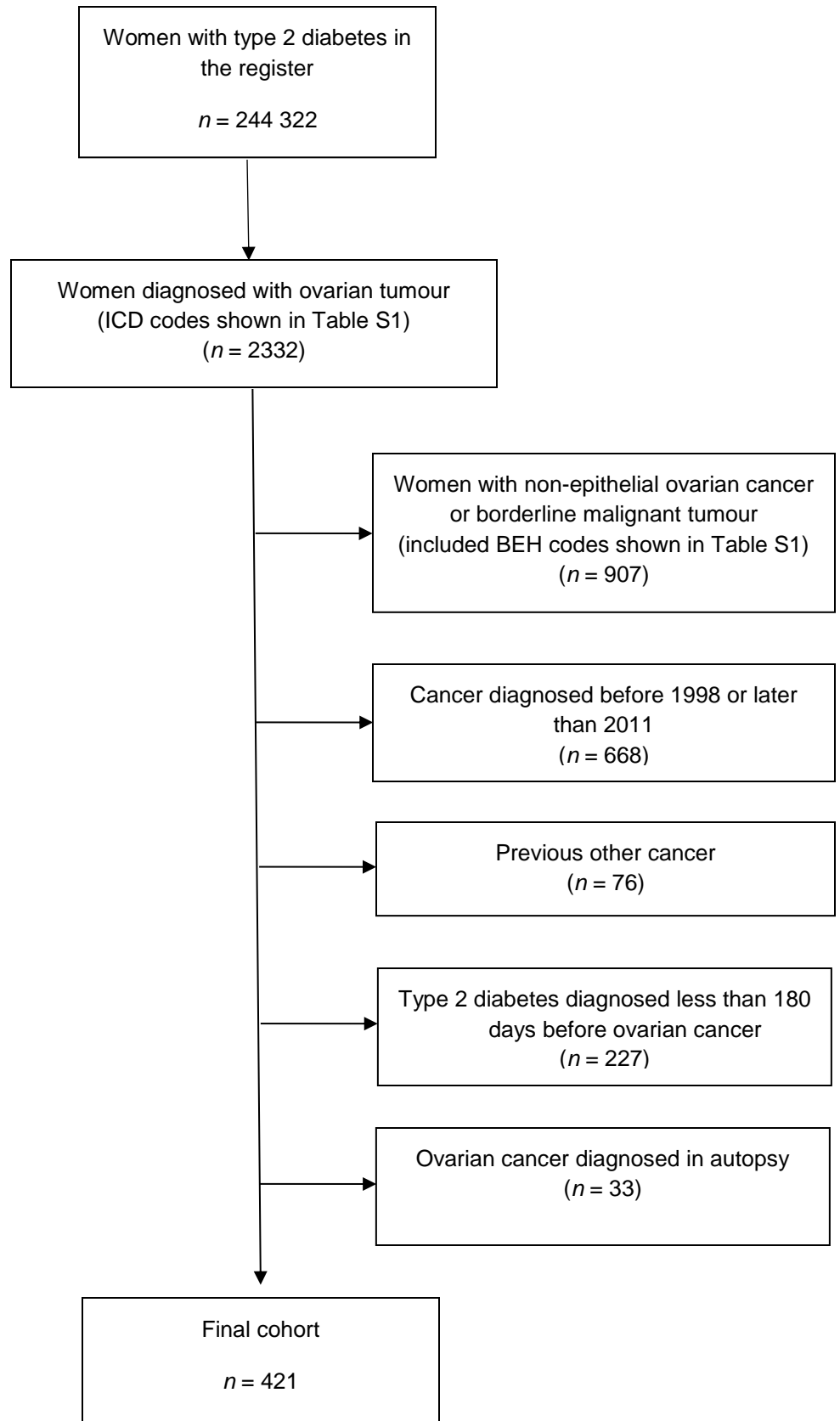


Table 1. Incidence rates of ovarian cancer (per 100,000 person-years), distribution of person-years at risk, and numbers (%) of cases and matched controls by age, duration of diabetes and medication use. Cases and controls were matched for age (± 182 days) and duration of diabetes (± 182 days).

Variable	Value	Incidence (per 100 000 person-years)	Person-years in cohort	Cases (%)	Controls (%)
Age (years)					
	40–49	12.7	47229	6 (2.0)	126 (2.1)
	50–59	28.9	127996	37 (12.2)	730 (12.0)
	60–69	51.4	194406	100 (33.0)	2000 (33.0)
	70–79	49.5	216225	107 (35.3)	2140 (35.3)
	80–89	35.9	142166	51 (16.8)	1023 (16.9)
	90–106	9.9	20260	2 (0.7)	41 (0.7)
Duration of diabetes (years)					
	1–<3	38.0	239473	91 (30.0)	1903 (31.4)
	3–<5	38.1	175744	67 (22.1)	1289 (21.3)
	5–<8	52.5	177254	93 (30.7)	1771 (29.2)
	8–<16	33.4	155811	52 (17.2)	1097 (18.1)
Metformin use					
	Ever	41.1	486197	200 (66.0)	4080 (67.3)
	Never	39.3	262085	103 (34.0)	1980 (32.7)
Other oral antidiabetic medication use					
	Ever	40.8	367964	150 (49.5)	2978 (49.1)
	Never	40.2	380319	153 (50.5)	3082 (50.9)
Insulin use					
	Ever	43.4	87654	38 (12.5)	658 (10.9)
	Never	40.1	660629	265 (87.5)	5402 (89.1)
Any antidiabetic medication use					
	Ever	42.0	606537	255 (84.2)	4979 (82.2)
	Never	33.9	141745	48 (15.8)	1081 (17.8)
Statin use					
	Ever	42.8	371806	159 (52.5)	3235 (53.4)
	Never	38.2	376476	144 (47.5)	2825 (46.6)

Table 2. Adjusted estimates of hazard ratios (HR, with 95 % confidence intervals, CI) for the association between ovarian cancer incidence and "ever use" of metformin and insulin compared with the use of other forms of oral antidiabetic medication, and the use (at any time) of statins compared with no use of statins at any time. The estimates are based on Poisson regression using the full-cohort data, and conditional logistic regression using the nested case-control data, both adjusted for age and duration of diabetes.

Ever use	Full cohort, HR (95% CI)	Case-control, HR (95% CI)
Metformin	1.02 (0.72-1.45)	0.91 (0.61-1.34)
Insulin	1.19 (0.73-1.93)	1.19 (0.72-1.97)
Statin	0.99 (0.78-1.25)	0.96 (0.75-1.23)

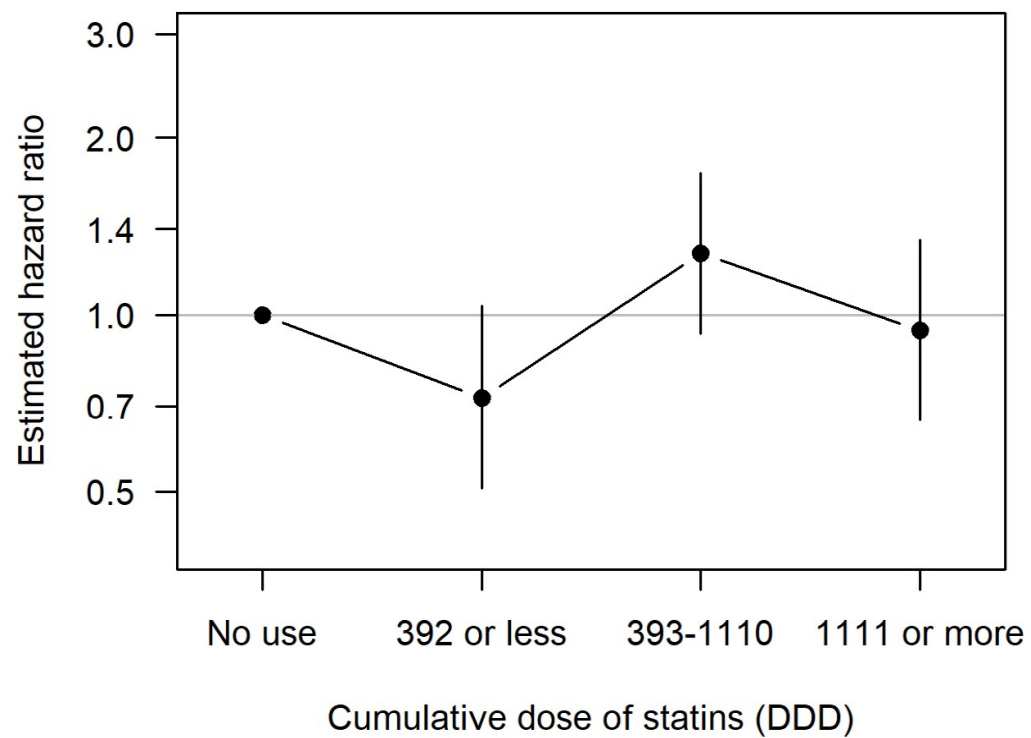
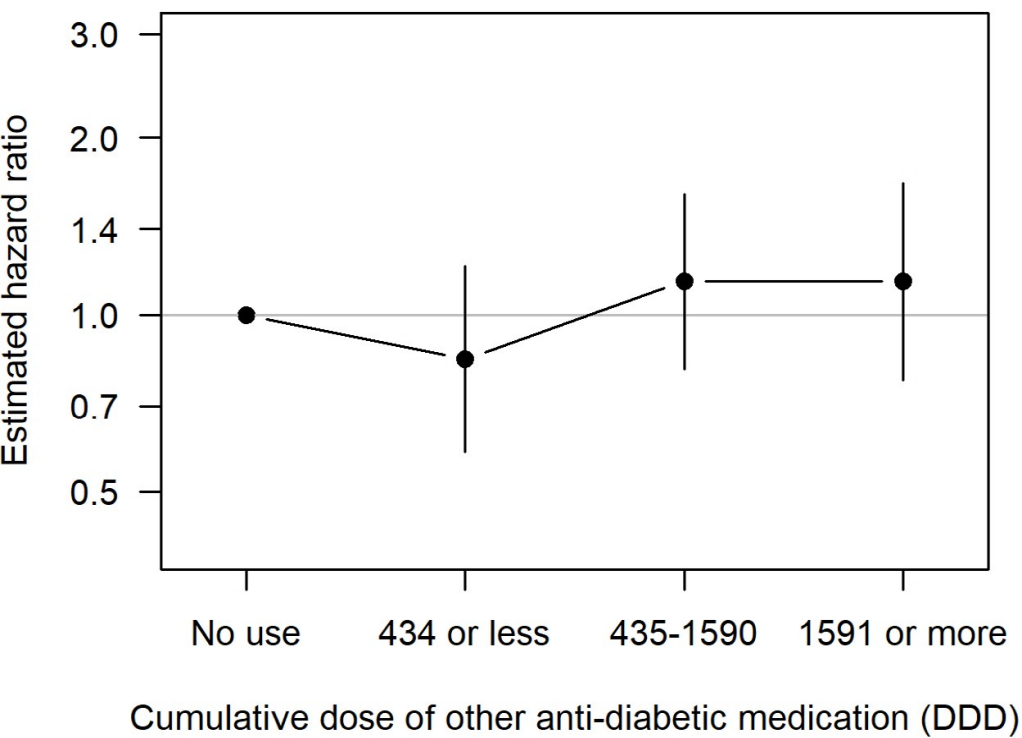
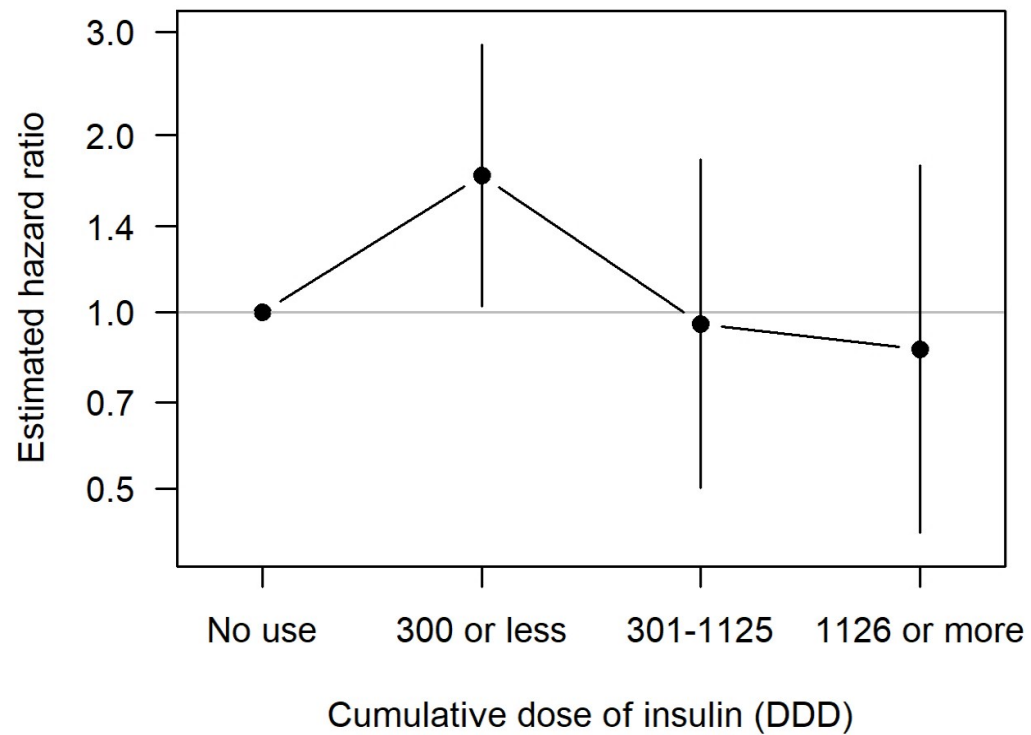
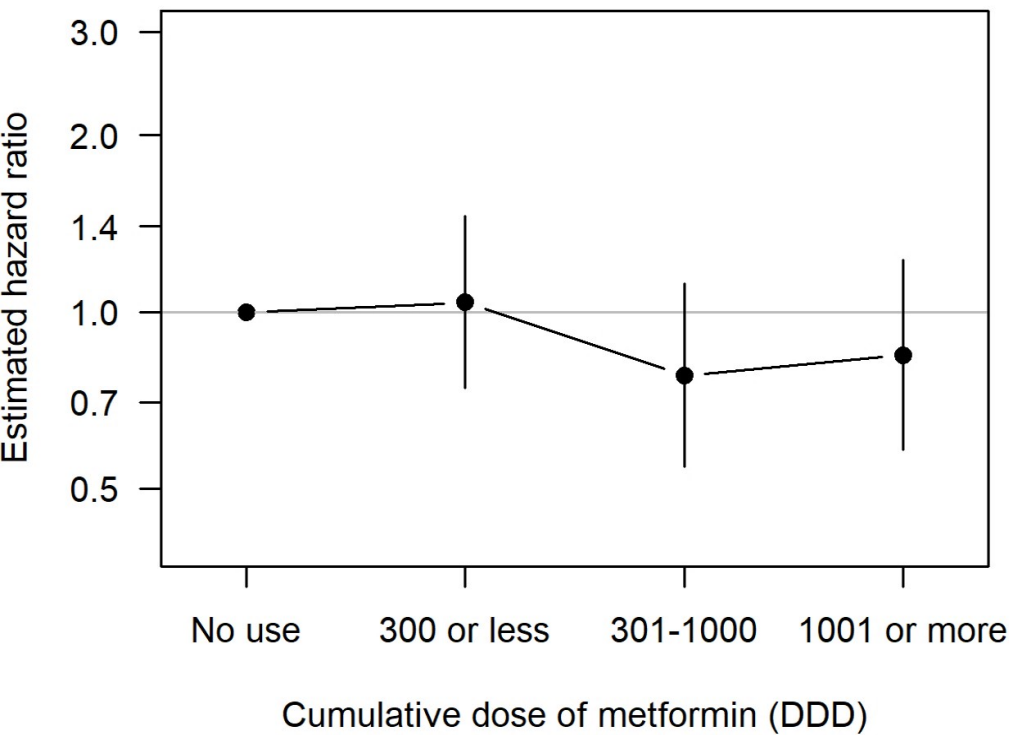


Table S1. ATC codes and percentages of other forms of oral antidiabetic medication and statins.

Medication	ATC codes	Controls (%)	Cases (%)
Other oral antidiabetic medication			
Sulphonylureas		92.6	94.7
	A10BB01		
	A10BB07		
	A10BB12		
Glitazones		11.0	10.0
	A10BG02		
	A10BG03		
DPP-4 inhibitors		2.9	2.7
	A10BH01		
	A10BH02		
	A10BH03		
Glinides		1.7	2.0
	A10BX02		
	A10BX03		
Fixed antidiabetic combinations		1.7	0
	A10BD04		
	A10BD05		
	A10BD07		
	A10BD08		
Statins			
Simvastatin	C10AA01	71.1	68.6
Atrovastatin	C10AA05	34.1	39.6
Rosuvastatin	C10AA07	10.0	17.0
Lovastatin	C10AA02	9.0	6.9
Pravastatin	C10AA03	9.0	10.7
Fluvastatin	C10AA04	2.3	3.8
Ezetimibe	C10AX09	2.3	3.8
Cerivastatin	C10AA06	0.6	0.6

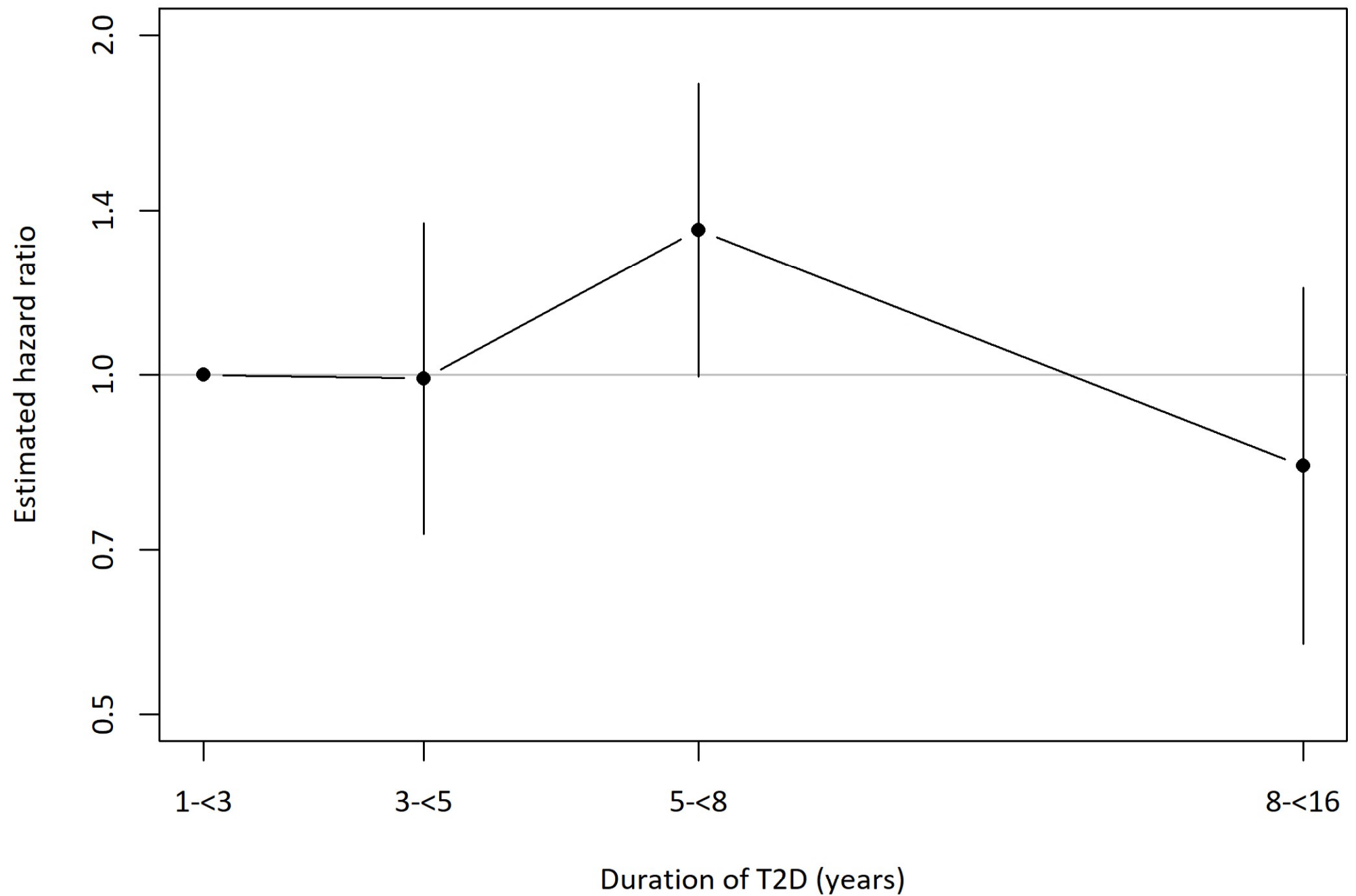


Figure S1. Estimated hazard ratios (bullets) with 95% confidence intervals (segments about the bullets) for ovarian cancer associated with different intervals of duration of T2D based on Poisson regression fitted on full cohort data.