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MORTALITY OF MIDLIFE WOMEN WITH SURGICALLY VERIFIED ENDOMETRIOSIS – A COHORT STUDY INCLUDING 2.5 MILLION PERSON-YEARS OF OBSERVATION

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MORTALITY OF MIDLIFE WOMEN WITH SURGICALLY VERIFIED ENDOMETRIOSIS – A COHORT STUDY INCLUDING 2.5 MILLION PERSON-YEARS OF OBSERVATION

Study question: Is the all-cause and cause-specific mortality increased among women with surgically verified endometriosis?

Summary answer: The all-cause and cause-specific mortality in midlife was lower throughout the follow-up among women with surgically verified endometriosis compared to the reference cohort.

What is known already: Endometriosis has been associated with an increased risk of comorbidities such as certain cancers and cardiovascular diseases. These diseases are also common causes of death however, little is known about the mortality of women with endometriosis.

Study design, size, duration: A nationwide retrospective cohort study of women with surgically verified diagnosis of endometriosis compared to the reference cohort in Finland (1987-2012). Follow-up ended at death or December 31st, 2014. During the median follow-up of 17 years, 2.5 million person-years accumulated.

Participants/materials, setting, methods:

49 956 women with at least one record of surgically verified diagnosis of endometriosis in the Finnish Hospital Discharge Register between 1987 and 2012 compared to a reference cohort of 98 824 age- and municipality-matched women. The age (mean±SD) of the endometriosis cohort was 36.4±9.0 and 53.6±12.1 years at the beginning and the end of the follow-up. By using the Poisson regression models the crude and adjusted all-cause and cause-specific

mortality rate ratios (MRR) and 95% confidence intervals (CI) were assessed. Calendar time, age, time since the start of follow-up, educational level, and parity adjusted were considered in the multivariate analyses.

Main results and the role of chance:

1656 and 4291 deaths occurred in the endometriosis and reference cohorts, respectively. A lower all-cause mortality was observed for the endometriosis cohort (adjusted MRR 0.73 [95% CI 0.69 to 0.77]) - there were four deaths less per 1000 women over ten years. A lower cause-specific mortality contributed to this: the adjusted MRR was 0.88 (95% CI 0.81 to 0.96) for any cancer; and 0.55 (95% CI 0.47 to 0.65) for cardiovascular diseases, including 0.52 (95% CI 0.42 to 0.64) for ischemic heart disease and 0.60 (95% CI 0.47 to 0.76) for cerebrovascular disease. Mortality due to alcohol, accidents and violence, respiratory, and digestive disease related causes was also decreased.

Limitations, reasons for causation:

These results limit to the women with endometriosis diagnosed in a surgery. In addition, the study does not extend into the oldest age-groups. The results might be explained by the characteristics and factors related to women's lifestyle, and/or increased medical attention and care received, rather than the disease itself.

Wider implications of the findings:

These reassuring data are valuable to women with endometriosis and to their health care providers. Nonetheless, more studies are needed to address the causality.

Study funding/competing interest:

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78 relation to the present work, all the authors have completed the disclosure form.

INTRODUCTION

Endometriosis is a chronic inflammatory disease affecting approximately 5 to 10% of fertile-aged women. It causes substantial individual and societal burden, comparable to other chronic diseases (Simoens, et al., 2012, Vercellini, et al., 2014). Chronic inflammation is linked to various adverse health outcomes, such as increased risk of cardiovascular disease, cancer, and neurodegenerative diseases such as Alzheimer's disease (Nogueira, et al., 2015).

Indeed, endometriosis has been linked to increased risk of several associated conditions, including malignant, autoimmune, rheumatoid, and cardiovascular diseases. There is also an increased risk of several cancers, especially endometrioid and clear cell types of ovarian cancers and less clearly that of melanoma, non-Hodgkin lymphoma and thyroid carcinoma (Kvaskoff, et al., 2015). The Nurse's Health study recently found that the risk of coronary heart disease is significantly increased (1.5 to 2 -fold) among women with laparoscopically diagnosed endometriosis. In addition to chronic inflammation, surgical and/or medical treatments of endometriosis may contribute to this increased risk (Mu, et al., 2016).

Ischemic heart disease has long been the leading cause of death worldwide, and cancer is the leading cause of death in younger women in the western world (Lozano, et al., 2012, Naghavi, et al., 2017). In the present study, we examined the risk of death in a large cohort of women with surgically verified endometriosis in comparison to age and municipality matched reference women using high

quality Finnish administrative and health registers (Gissler and Haukka, 2004, Pukkala, et al., 2018, Sund, 2012). There is only one previous Swedish study assessing cancer survival in women with endometriosis (Melin, et al., 2011).

MATERIALS AND METHODS

Study population

To identify surgically diagnosed cases, all endometriosis-associated diagnoses (International Classification of Diseases version 9 [ICD-9 1987-1995]: 6171A, 6172A, 6173A, 6173B, 6174A, 6175A, 6176A, 6178X, 6179X; version 10 [ICD-10 1996-2012]: N80.1-N80.6, N80.8, N80.80, N80.81, N80.89, N80.9), as the main or subsidiary diagnosis, in combination with relevant concomitant surgical codes from 1987 to 2012 (n=49 956), were identified from the Finnish Hospital Discharge Register. The managing clinician sets the primary and secondary ICD codes for each procedure according to their clinical relevance. Adenomyosis as a sole diagnosis was not included. The index day was set to the day of discharge from the first hospital episode fulfilling the definition of surgically verified endometriosis.

There were altogether 57 713 endometriosis diagnoses among 49 956 women in the index procedure. Peritoneal endometriosis was the most common diagnosis (n=26 299, 46%) followed by ovarian endometriosis (n=24 343, 42%), other or

unknown endometriosis (n=3578, 6%) and deep infiltrating endometriosis (n=3493, 6%).

The reference cohort (n=98 824) was randomly drawn by a computer from the Finnish Population Information System. The reference cohort was first constructed by selecting, for each endometriosis patient, two women who were alive, lived in the same municipality and were of similar age on the index date, and had no surgically verified endometriosis according to the Finnish Hospital Discharge Register records over the period of 1987-2012 and no hospital admissions due to endometriosis 1983-1987. The final reference cohort included one to two women for each endometriosis patient fulfilling these criteria.

Data sources

In Finland administrative and health data for the entire population has been collected for decades using well established and high standard procedures (Gissler and Haukka, 2004, Pukkala, et al., 2017, Sund, 2012). A unique personal identity code, issued to every resident in Finland since 1964-1968, secures a reliable data recording and allows data linkage since 1969.

The Finnish Hospital Discharge Register (FHDR) includes personal identity codes, codes of diseases according to the ICD, and dates for each hospital visit since 1967 from both general and private sector inpatients, as well as for day-surgeries from 1994 onwards (www.thl.fi/en/web/thlfi-en). Validity of the different diseases in the FHDR has been evaluated as satisfactory to good in

numerous studies. The quality assessment of FHDR concerning the present cohort was performed prior to initiating this study (Saavalainen, et al., 2018).

The Finnish Population Information System, maintained by the Finnish Population Register Centre, is a computerized national register that contains basic information on permanent residents, such as date of birth and death, address, and biological children of permanent residents (www.vrk.fi/en/frontpage).

Statistics Finland is a public authority that collects and maintains administrative data, such as the population census and the Cause-of-Death Register (www.stat.fi/index_en.html). The latter includes the date of death and underlying cause of death according to the disease or circumstance (accident, act of violence) leading to death. The cause of death is determined according to the rules of the ICD-10 compiled by the World Health Organization. The causes-of-death are given by the treating physician and controlled regionally and at Statistics Finland.

Cohort characteristics

The demographic characteristics of the whole study population (n=148 780) were obtained from Statistics Finland. The population census data contains data on socioeconomic status, education, and profession. Because the data on occupation and socioeconomic status were limited to the census years (1995, 2000, and 2004-2012) only, we used the highest educational level from the 2014

178 census as a proxy for socioeconomic status. In the analysis, the highest
179 education level reached was treated as a categorical variable with four
180 categories: academic degree (bachelor, master, and doctoral); tertiary (short-
181 cycle tertiary); upper secondary; and primary (primary and unknown).
182
183 The baseline calendar time, removal of gynecological organs, and parity status
184 were represented as dichotomous variables. The baseline calendar time was
185 divided into two periods according to the ICD coding system (ICD-9 in 1987-
186 1995, and ICD-10 in 1996-2012). Based on the data on removal of the
187 gynecological organs from the Finnish Hospital Discharge Register (1983-
188 2012), we identified those with any gynecological organ removed before or at
189 the index procedure. The baseline parity status was defined according to the
190 information on live births obtained from the Population Register as at least
191 one live birth before or at the index date and was then updated according to
192 the follow-up information.
193
194 **Follow-up and outcomes of interest**
195
196 Women were followed from the index day until death or until the end of
197 follow-up on December 31st, 2014, which ever came first. The outcome of
198 interest was the mortality from any cause, as well as the cause-specific
199 mortality based on the underlying cause of death. The specific causes of death
200 were studied in groups formed according to the 54-group short-list of causes

of death by Statistics Finland (Supplementary Table SI) where the alcohol-related deaths are separately presented as their incidence in Finland is high.

Statistical analysis

For each outcome of interest, the crude mortality rate was calculated as the number of deaths divided by person time at risk, and the exact 95% confidence intervals (CIs) were assessed based on Poisson rates. For any cause mortality, we assessed both crude absolute and relative rate differences (ratio) in mortality rate between the cohorts. To allow for assessment of time-varying covariates, such as age, time since the index date, and parity, the individual follow-up time was split into the smaller bands. We calculated adjusted all-cause and cause-specific mortality rate ratios (MRRs) with 95% CIs by using multivariate Poisson model. We controlled for age and time since the index day as modelled by spline functions, the highest educational level and baseline calendar time (Model 1), and further for parity as assessed in a time-dependent manner (Model 2). The area of residence at the time of first endometriosis surgery was not statistically significant and therefore was not included. To study the changes in the all-cause MRRs during the follow-up, we plotted the adjusted MRR with 95% CI from the Model 2 along the time since the index date. In addition, we used the (multivariate) Poisson model with identity link to calculate the crude (adjusted) absolute rate differences with their 95% CIs for death from all-causes and major specific causes.

We performed several sensitivity analyses. To check whether the results were similar across all ages at death we calculated and plotted age-specific MRRs with 95% CIs for the all-cause mortality by six age groups (<30, 30-39, 40-49, 50-59, 60-69, and ≥70 years at death). To assess the potential heterogeneity in the MRRs according to the baseline gynecological organ removal in women with surgically verified endometriosis, we divided the endometriosis cohort into two groups, those with and without the baseline gynecological organ removal. By substituting the binary variable for endometriosis (no/yes) in Model 2 by a variable with three categories (no/yes without removal/yes with removal), we compared the endometriosis subgroups to the reference cohort, from which we excluded women who had undergone gynecological organ removal before beginning of the follow-up.

We set statistical significance level at 5% and considered the results with p-values < 0.05 as statistically significant. All statistical analyses were performed using R statistical software version 3.5.0 (www.r-project.org), with the Epi-package for splitting the individual follow-up (Plummer and Carstensen, 2011), and the Forestplot-package for the graphical output (Gordon and Lumney, 2017).

Ethical approval

Before initiation this study was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa (238/13/03/03/2013). Permissions to utilize

the data and to perform the linkages were provided by the National Institute for Health and Welfare (THL/546/5.05.00.2014), the Population Register Centre (D1794/410/14), and Statistics Finland (Dnro TK53-547-14).

RESULTS

All-cause mortality

Altogether 2.5 million person-years (34% in the endometriosis cohort and 66% of the control cohort) of follow-up accumulated during the mean follow-up time of 16.8 (standard deviation [SD] ±7.3) years. The mean age of the study population at the end of the follow-up was 53.6 (SD ±12.1) years. The demographic characteristics of endometriosis and reference cohorts are shown in Table I. The person-years, number of deaths, and mortality rates for the entire study population including both cohorts are shown in Supplementary Table SII by calendar time and age.

There were altogether 1656 and 4291 deaths, and the mortality rate was 19.6 and 25.9 per 1,000 women over ten years among endometriosis and reference cohorts. Of the observed deaths in the endometriosis cohort 817 (49%) were due to malignant neoplasms, 277 (17%) due to diseases of the circulatory system, and 199 (12%) due to accidents and violence. For both cohorts, the number of deaths, the crude all-cause and cause-specific MRs are shown in Supplementary Table SIII.

Table II shows the crude and adjusted all-cause and cause-specific MRRs with their 95% CIs from the Model 1 and Model 2. The change in the MRRs after additional adjustment for live births was minor and therefore, the "adjusted" refers here to Model 2. In the endometriosis cohort, we observed a lower risk of all-cause mortality (adjusted MRR 0.73 [95% CI 0.67 to 0.77]). The adjusted absolute rate difference in all-cause mortality was -4.27 (95% CI -6.24 to -2.30) among 1000 women over ten years with surgically verified endometriosis compared to the women in the reference cohort.

The adjusted relative difference in all-cause mortality decreased over time remaining, however, was statististically significant 24 years (Figure I). Figure II illustrates the adjusted MRRs for any and several specific causes of death.

Cancer mortality

The mortality rate of any cancer was 9.7 and 10.7 per 1,000 women over ten years among the endometriosis and reference cohorts, respectively. The adjusted MRR (0.88 [95% CI 0.81 to 0.96]) showed a lower mortality due to any cancer in the endometriosis cohort as compared to the reference cohort (Table II). The adjusted absolute rate difference of death due to any cancer was -0.57 (95% CI -1.63 to 0.50) per 1000 women over ten years between the endometriosis and reference cohorts.

Cardiovascular mortality

299

300 The mortality rate due to diseases of the circulatory system was 3.3 and 5.5 per
301 1000 women over ten years among the endometriosis and reference cohorts.
302 The adjusted MRR (0.57 [95% CI 0.50 to 0.65]) was significantly lower in the
303 endometriosis than in the reference cohort, and this difference was consistent
304 across specific diseases, including cardiovascular diseases, ischemic heart
305 disease, and cerebrovascular disease (Table II). The adjusted absolute rate
306 difference was -0.02 (95% CI -0.12 to 0.08) per 1000 women over ten years
307 between the endometriosis and reference cohorts.

308

309 **Other causes of mortality**

310

311 The mortality rate due to alcohol-related causes (alcohol-related diseases and
312 accidental poisoning by alcohol) was 1.0 and 2.3 per 1000 women over ten years
313 among the endometriosis and reference cohorts (adjusted MRR 0.42 [95% CI
314 0.33 to 0.53]). Mortality due to other causes of death, such as diseases of the
315 respiratory and digestive systems, accidents and violence was also lower in the
316 endometriosis cohort. No differences in mortality were found to be due to:
317 dementia or Alzheimer's disease combined; other diseases of the nervous system
318 and sense organs; or suicide (Table II, Figure II).

319

320 **Sensitivity analysis**

321

322 According to the results of sensitivity analysis assessing the age-specific relative
323 difference in all-cause mortality between the cohorts, the MRRs were consistent

across the entire age range at death covered by the study except the youngest age group (<30 years, 49 deaths [Figure III]). The results of sensitivity analysis according to the status of baseline gynecological organ removals suggested significant differences in adjusted MRR only with breast and ovarian cancer (Supplementary Table SIV). The adjusted MRR of breast cancer was significantly decreased only in women with endometriosis and baseline gynecological organ removals as compared to the reference population, of which we excluded women with gynecological organ removals before or at the index date. On the contrary, the MRR of ovarian cancer was significantly increased only in women without gynecological organ removals in endometriosis cohort compared to the women in the reference cohort who had no previous gynecological organ removals. In all-cause MRR, or in MRR due to cardiovascular disease, accidents and violence, or suicides no difference was seen.

DISCUSSION

The all-cause mortality in midlife was lower throughout the follow-up among women with surgically verified endometriosis compared to the reference cohort. The absolute difference was low - four fewer deaths occurred among 1000 women over ten years of follow-up in endometriosis patients. Endometriosis is associated with an increased risk of several common diseases, also known as common causes of death. However, even if morbidity is increased, mortality due to these conditions may be decreased. Nevertheless, even after adjustments mortality due to these conditions was decreased, i.e. deaths due to any cancer

and cardiovascular conditions including ischemic heart disease and cerebrovascular disease. We also found a decreased risk of death due to alcohol-related causes, accidents and violence, and diseases of the digestive and respiratory system.

The strengths of this study include the surgically diagnosed endometriosis disease, the large, population-based cohort of women, and the long follow-up (nearly three decades of calendar time and a follow-up of 2.5 million person-years). Finland has a long history of administrative data collection. Nationwide health and social registers have provided an important data source for epidemiological research. Moreover, due to the high-quality nationwide population-based registers, the completeness and validity of the data are reliable (Gissler and Haukka, 2004, Pukkala, et al., 2017, Sund, 2012). The registers also allowed us to adjust for many demographic factors that are important when assessing mortality (Forouzanfar, et al., 2016, Jensen, et al., 2017, Mackenbach, et al., 2016, Stringhini, et al., 2017). In addition, previous knowledge of the all-cause and cause-specific mortality in women with endometriosis is scarce.

Several important lifestyle factors, such as smoking, alcohol consumption,-body mass index, or use of medications could not be adjusted for as they do not exist in our register-based data. These risk factors contribute significantly to the development and prognosis of several illnesses, and therefore also to deaths – therefore the residual confounding cannot be ruled out (Danaei, et al., 2009, Di Angelantonio, et al., 2016, Flegal, et al., 2013). In previous studies, endometriosis diagnosis has been associated with lower body mass index, but the results have

been inconsistent for alcohol consumption and tobacco smoking (Parazzini, et al., 2013, Bravi, et al., 2014, Shafrir, et al. 2018). We found lower risk of death due to alcohol-related causes in women diagnosed with endometriosis. In addition, the decreased mortality due to accidents and violence might also reflect the safer lifestyle of women with endometriosis. However, there was no significant difference in the risk of lung cancer mortality, which often reflects the smoking habits of the study population.

The present study may also be subject to selection bias, bias by indication, detection bias or reverse causality. First, the selection bias exists as the procedural data was not collected until 1987 and therefore, some women in the reference cohort may have undergone the endometriosis procedures prior to that. Moreover, the reference cohort is likely to include women with undiagnosed endometriosis (approx. 2%; Zondervan, et al., 2002) and endometriosis without surgical verification.

Uneven access to health care results often in another selection bias. There are also some inequalities in access to health care in Finland (Kangas and Blomgren, 2014). Moreover, the access to the specialized medical care may depend on patient's awareness and persistence. This may cause a selection bias in our study. In the analysis, we adjusted for the education level that is known to be associated with the socioeconomic status, health behavior and risk contexts. Endometriosis is typically diagnosed after a delay of approximately seven years (Nnoaham, et al., 2011). Thus, women in the endometriosis cohort are likely to have been rather persistent in seeking medical advice and help. This may apply

399 to other health issues as well. In addition, receiving an endometriosis diagnosis
400 and medical attention might alter the overall behavior towards healthier
401 lifestyle. It is also possible that some of the important risk factors, such as alcohol
402 abuse, restrain women from seeking medical help. Moreover, to be eligible for
403 operative treatment is likely to exclude several serious conditions, and
404 preoperative evaluation might reveal other pre-existing diseases as well as
405 increased medical attention postoperatively leads to a situation referred as
406 selection and detection bias.
407
408 The indication bias is caused by limiting the study cohort to women with
409 endometriosis eligible for operative treatment, although the indications were not
410 otherwise limited as we also included incidental diagnosis of endometriosis
411 (subsidiary diagnosis 35% of all diagnosis). In addition, confounding by
412 indication might also be caused by the presence of comorbidities between the
413 cohorts, not adjusted in the present study.
414
415 Moreover, live births were taken into account as nulliparous women are known
416 to have increased risk of death (Zeng et al., 2016). However, the data on
417 infertility was not available. Furthermore, the former data have shown women
418 with assisted reproductive techniques to have decreased risk of death although
419 the recent study have shown that there is a healthy patient effect - the risk of
420 death returns to normal after ten years. (Braat, et al., 2010, Vassard, et al., 2018)
421
422 Women with endometriosis are likely to use more non-steroidal anti-
423 inflammatory drugs and hormonal medications such as oral contraceptives. Non-

steroidal anti-inflammatory drugs are known to decrease the risk of death due to ovarian, colon and breast cancer and moreover, also the deaths due to myocardial infarction (Verdoodt, et al., 2017, Din, et al., 2010, Huang, et al., 2015, Olsen, et al., 2011). Furthermore, oral contraceptives are reported to decrease the overall risk of death and for example deaths due to ovarian cancer (Hannaford, et al., 2010, Beral, et al., 2008). The use of these medications might contribute in part to the decreased mortality among women with endometriosis.

Another limitation in our study is that it fails to reliably extend into older age groups. The mean age when entering to the study cohorts was 36 years, and after the follow-up was 53 years. Therefore, data on women older than 75 years of age are limited. Many diseases have their highest incidences in older ages, including many cancers, dementia, or Alzheimer's disease (Naghavi, et al., 2017). Thus, our results can only be generalized to midlife women.

The potential presence of several types of bias may explain at least part – or even entire – of the lower all-cause mortality seen among women with endometriosis. A difference in the overall mortality between the cohorts was present already at the time of the index surgery and persisted 24 years. This suggests the difference to be drawn by the factors other than endometriosis *per se*. Thus, the present results can be applied only to midlife women with surgically verified endometriosis and caution is needed when interpreting the results in terms of causality.

448 During the study period the two most common causes of death among working
449 aged Finnish women were neoplasms and diseases of the circulatory system,
450 followed by causes related to alcohol, accidents, and suicides. The risk of death
451 due to any cancer was decreased among women with surgically verified
452 endometriosis. After adjustments for potential confounders, there were 12%
453 fewer cancer deaths in the endometriosis cohort. At baseline any gynecological
454 organ removal (hysterectomy, unilateral or bilateral oophorectomy or both)
455 occurred in 38% of the endometriosis cohort and 3% of the reference cohort.
456 Even though these procedures cannot be separated from endometriosis
457 treatment, they account partly for the decreased cancer deaths. Indeed, the
458 sensitivity analysis showed that the adjusted MRR for ovarian cancer was
459 increased only in women with endometriosis who had no baseline gynecological
460 organ removals. In addition to the sensitivity analyses, the proportion of the
461 association between endometriosis and mortality explained by the various
462 treatments or interventions (including organ removal) have not been addressed
463 in this analysis. As morbidity studies to date suggest, treatments, and in
464 particular organ removal, may play an important role on the causal pathway(s).
465
466 The association of endometriosis and favorable prognosis of ovarian cancer has
467 been reported previously (Melin, et al., 2011, Kim, et al., 2014). The focus of the
468 present study was, however, on the mortality in women with endometriosis as
469 followed from the index surgery due to endometriosis but not from cancer
470 diagnosis. Therefore, the results of our study cannot be interpreted in terms of
471 cancer survival.
472

Mortality due to breast cancer was decreased in women with surgically verified endometriosis compared to the reference cohort before and after adjustment for important risk factors, such as parity. Parity and breast feeding are known to decrease the risk of breast cancer (Lambertini, et al., 2016, Victora, et al., 2016). Moreover, the risk of breast cancer and breast cancer deaths are also reduced by oophorectomy (Nichols, et al., 2011, Parker, et al., 2013). The sensitivity analysis included all gynecological organ removals (hysterectomy and/or oophorectomy/-ies) and showed that only women with gynecological organ removals had significantly decreased MRR for breast cancer. Hormonal replacement therapy, or the lack of it, might affect breast cancer mortality, but unfortunately, we lacked data on the possible use of hormonal replacement therapy in our study cohort. The numbers of deaths due to other cancers are too few to reliably assess the possible differences associated to endometriosis.

Compared to the reference cohort, 45% fewer deaths due to cardiovascular diseases were reported for women with surgically verified endometriosis. This finding was further strengthened following disease specific calculations for ischemic heart disease and cerebrovascular disease, where the adjusted risk of death was also decreased. Moreover, in the sensitivity analysis gynecological organ removals had no effect on the difference. Recent studies have shown that oophorectomy and early menopause increase the mortality for cardiovascular disease (Evans, et al., 2017, Gong, et al., 2016, Muka, et al., 2016, Mytton, et al., 2017). In addition, in a recent North American study even hysterectomy without oophorectomy when performed to women aged 35 years or under increases the risk of cardiovascular conditions (Laughlin-Tomaso, et al., 2018). However, the

role of parity or hormonal replacement therapy is unclear (Boardman, et al., 2015, Jacobs, et al., 2012, Magnus, et al., 2017, Santen, et al., 2010, Tuomikoski and Mikkola, 2014). No adjustments were made in this study for the major cardiovascular risk factors - hypertension, diabetes, and hypercholesterolemia - nor for lifestyle factors, due to the unavailability of such information (Mosca, et al., 2011). The decrease in cardiovascular mortality might partly relate to the risk factors. Studies with longer follow-up times are likely to clarify these results as cardiovascular diseases occur more often in advanced age.

Alzheimer's disease has been linked to chronic inflammation (Nogueira, et al., 2015). However, according to a recent Canadian study mortality rate due to Alzheimer's disease in women increases only after 75 years of age and the mean age at death is 86 years (Park, 2016). In the present study, the mean age of women at the end of follow-up was 54, precluding from a reliable assessment of the potential relationship between endometriosis and Alzheimer's disease.

In conclusion, the overall mortality in midlife was lower in women with surgically verified endometriosis when compared to the reference cohort. The adjusted cause-specific mortality due to cancer, circulatory diseases, cardiovascular diseases, alcohol related causes, accidents and violence, and diseases of the digestive and respiratory systems, were all decreased. We speculate that the decreased mortality is significantly due to different characteristics and factors related to women's lifestyle, and/or increased medical attention and care received among women with surgically verified endometriosis. There is a need for more studies on this issue.

AUTHORS' ROLES

All authors contributed to the study idea and planning the study design. The data linkages, management and statistical analyses were comprised by AB and JH. The interpretation of the data and results were contributed by all authors. LS drafted the article in supervision by OH. All authors reviewed and revised the article and approved the final version.

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CONFLICT OF INTEREST

None.

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Table I. Baseline characteristics of the women in the cohort of surgically verified endometriosis and in the reference cohort.

Characteristic	Endometriosis cohort[a)] *n* (%) (*n*=49 956)	Reference cohort *n* (%) (*n*=98 824)
Year of entry in the cohort		
1987-1995 (ICD-9)	23 655 (47.4)	46 867 (47.4)
1996-2012 (ICD-10)	26 301 (52.7)	51 957 (52.6)
Age at entry in the cohort years median (IQR)		
1987-1995	38.6 (31.5, 44.1)	38.6 (31.5, 44.1)
1996-2003	35.1 (28.7, 43.3)	35.1 (28.7, 43.3)
2004-2012	33.4 (28.2, 41.1)	33.4 (28.2, 41.1)
Age at entry in the cohort		
12-19	526 (1.1)	1053 (1.1)
20-29	12 690 (25.4)	25 152 (25.5)
30-39	18 044 (36.1)	35 599 (36.0)
40-49	15 287 (30.6)	30 260 (30.6)
50-59	2984 (6.0)	5918 (6.0)
60-69	339 (0.7)	670 (0.7)
70-79	74 (0.1)	148 (0.2)
80-85	12 (0.0)	24 (0.0)
Residence[b)]		
Urban municipality	34 161 (68.4)	67 613 (68.4)
Densely populated	8540 (17.1)	16 861 (17.1)
Rural	7255 (14.5)	14 350 (14.5)
Profession at baseline[c)]		
Managers	333 (2.1)	535 (1.7)
Professionals	2632 (16.6)	4498 (14.4)
Technicians	3005 (19.0)	4891 (15.6)
Clerical	1555 (9.8)	2791 (8.9)
Service and sales workers	3296 (20.8)	6131 (19.6)
Skilled agricultural, forestry and fishery workers	219 (1.4)	522 (1.7)
Craft and related trades workers	254 (1.6)	466 (1.5)
Plant and machine operators, assemblers	493 (3.1)	912 (2.9)
Elementary occupations	825 (5.2)	1760 (5.6)
Armed forces	6 (0.0)	8 (0.0)
Unknown	229 (1.5)	550 (1.8)
Student, pensioner or unemployed	2511 (15.9)	6052 (19.3)
Missing	471 (3.0)	2208 (7.1)
Socioeconomic status[c)]		
Self-employed	711 (4.5)	1658 (5.3)
Upper-level employees	2972 (18.8)	5302 (17.0)
Lower-level employees	6830 (43.2)	12 018 (38.4)
Manual workers	2455 (15.5)	5222 (16.7)
Students	922 (5.8)	2385 (7.6)
Pensioners	346 (2.2)	1039 (3.3)
Unemployed	1243 (7.9)	2628 (8.4)
Unknown	320 (2.0)	1011 (3.2)
Missing	0 (0)	0(0)
Highest education[d)]		
Academic	12 519 (25.1)	23 341 (23.7)
Doctoral	592 (1.2)	1066 (1.1)
Master	6147 (12.3)	11 411 (11.6)
Bachelor	5780 (11.6)	10 864 (11.0)
Short-cycle tertiary	9870 (19.8)	17 586 (17.8)
Upper secondary	19 140 (38.3)	38 934 (39.4)
Primary	8427 (16.9)	18 963 (19.2)

Primary	7654 (15.3)	16 721 (16.9)
Unknown	773 (1.6)	2242 (2.3)
Any gynecological organ removal at index day or before	18 869 (37.8)	2955 (3.0)
Hysterectomy	5456 (10.9)	1931 (2.0)
Unilateral or bilateral oophorectomy	4303 (8.6)	415 (0.0)
Hysterectomy with unilateral or bilateral oophorectomy	9110 (18.2)	609 (0.1)
History of live birth at baseline	24 524 (49.1)	67 218 (68.0)

ICD, International Classifications of Diseases. IQR, Interquartile range.

[a)] Surgically verified endometriosis.

[b)] Determined in Statistics Finland: Urban, city; densely populated, area where 200 people or more are living nearby; rural, under 200 people living nearby, usually over 200 metres between the buildings.

[c)] Those of working age 18-64 entering to the cohort during 1995, 2000, 2004-2012.

[d)] The highest education level according to statistics of 2014.

Table II. MRR for endometriosis versus the reference cohort: number of deaths in endometriosis cohort and the crude and the adjusted MRRs in women with endometriosis compared to the reference cohort with their 95% CI per 10 000 person-years.

Cause of death	Deaths in endometriosis cohort (*n*)	Crude MRR (95% CI)	Adjusted MRR (95% CI), Model 1	Adjusted MRR (95% CI), Model 2
All causes	1 656	0.76 (0.72-0.80)	0.77 (0.72-0.81)	0.73 (0.69-0.77)
Malignant neoplasms	817	0.91 (0.83-0.98)	0.91 (0.84-0.99)	0.88 (0.81-0.96)
Stomach	40	0.98 (0.67-1.44)	0.99 (0.68-1.45)	0.96 (0.66-1.41)
Colorectal	76	1.12 (0.85-1.49)	1.13 (0.86-1.50)	1.11 (0.84-1.47)
Pancreas	51	0.76 (0.55-1.05)	0.76 (0.55-1.05)	0.75 (0.54-1.03)
Trachea, bronchus, lung	103	1.04 (0.82-1.33)	1.06 (0.84-1.35)	1.06 (0.84-1.35)
Breast	198	0.84 (0.71-0.99)	0.83 (0.71-0.98)	0.81 (0.68-0.95)
Uterus	20	0.70 (0.42-1.17)	0.69 (0.41-1.14)	0.61 (0.37-1.03)
Ovary	77	1.09 (0.82-1.44)	1.09 (0.82-1.44)	1.01 (0.77-1.34)
Dementia and Alzheimer's disease	47	1.47 (1.01-2.14)	1.43 (0.98-2.09)	1.39 (0.95-2.03)
Other diseases of the nervous system and sense organs	60	0.94 (0.69-1.27)	0.94 (0.69-1.27)	0.87 (0.64-1.18)
Diseases of the circulatory system[a)]	277	0.60 (0.52-0.68)	0.60 (0.53-0.69)	0.57 (0.50-0.65)
Cardiovascular diseases	205	0.58 (0.50-0.68)	0.59 (0.50-0.69)	0.55 (0.47-0.65)
Ischemic heart diseases	115	0.55 (0.45-0.68)	0.56 (0.45-0.69)	0.52 (0.42-0.64)
Cerebrovascular diseases	90	0.63 (0.50-0.80)	0.63 (0.50-0.80)	0.60 (0.47-0.76)
Diseases of the respiratory system	31	0.43 (0.29-0.63)	0.44 (0.30-0.65)	0.42 (0.29-0.63)
Diseases of the digestive system[a)]	29	0.62 (0.41-0.94)	0.63 (0.42-0.96)	0.59 (0.39-0.90)
Alcohol related diseases and accidental poisoning by alcohol	82	0.43 (0.34-0.54)	0.44 (0.35-0.56)	0.42 (0.33-0.53)
Accidents and violence [b)]	219	0.85 (0.72-1.00)	0.87 (0.74-1.02)	0.80 (0.68-0.94)
Accidents total[b)]	92	0.72 (0.57-0.91)	0.73 (0.58-0.93)	0.68 (0.54-0.87)
Suicides and sequalae of intentional self-harm	114	1.07 (0.85-1.35)	1.10 (0.87-1.38)	1.00 (0.79-1.26)
Other causes[c)]	48	0.61 (0.44-0.84)	0.63 (0.45-0.86)	0.55 (0.40-0.77)

[a)] Excluding diseases caused by alcohol. [b)] Excluding accidental poisonings by alcohol. [c)] Diseases not included in other categories.

Results presented when number of deaths exceeded twenty per specific death cause.
The adjustable variables used in multivariable Poisson analysis:
Model 1: Adjusted for the calendar time (ICD-9 or ICD-10) at baseline, the highest educational level (four levels), and the age and time-on-study as time dependent covariates modelled by cubic spline.
Model 2: Model 1 variables and in addition live births as time dependent dichotomous (no/yes) variable.

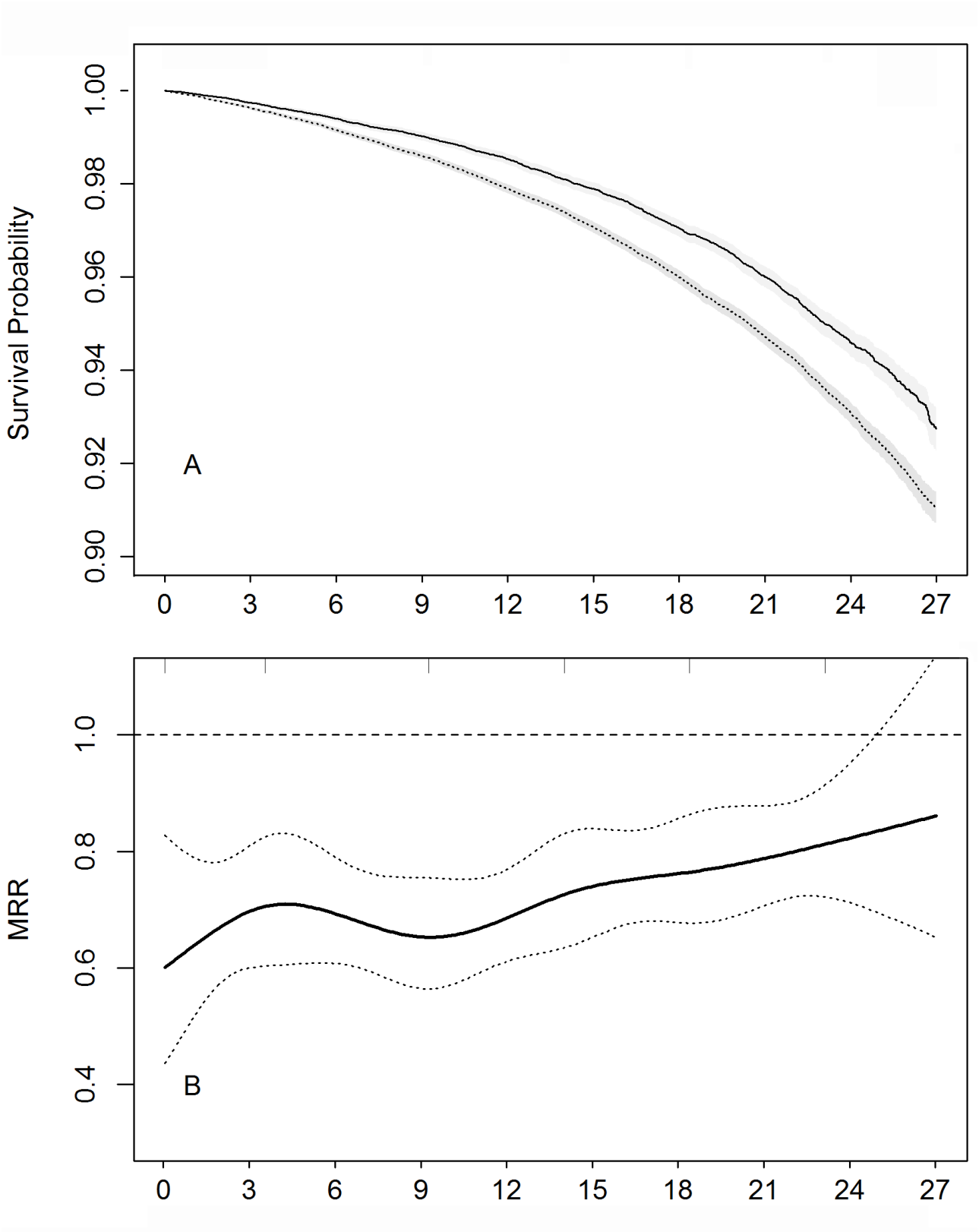

Figure I. Upper figure: The Kaplan-Meier survival probability. The bold solid line refers to endometriosis cohort and the dotted lines to reference cohort with shadowed 95% confidence intervals (CI). Lower figure: The adjusted (Model 2) all-cause mortality rate ratio as spline function of follow-up time (solid line) with 95% CIs (dotted lines) for the endometriosis cohort as compared to the reference cohort. The knots for the spline function (rugs at top) were set at quantiles (10%, 30%, 50%, 70%, 90%) calculated for the time at death.

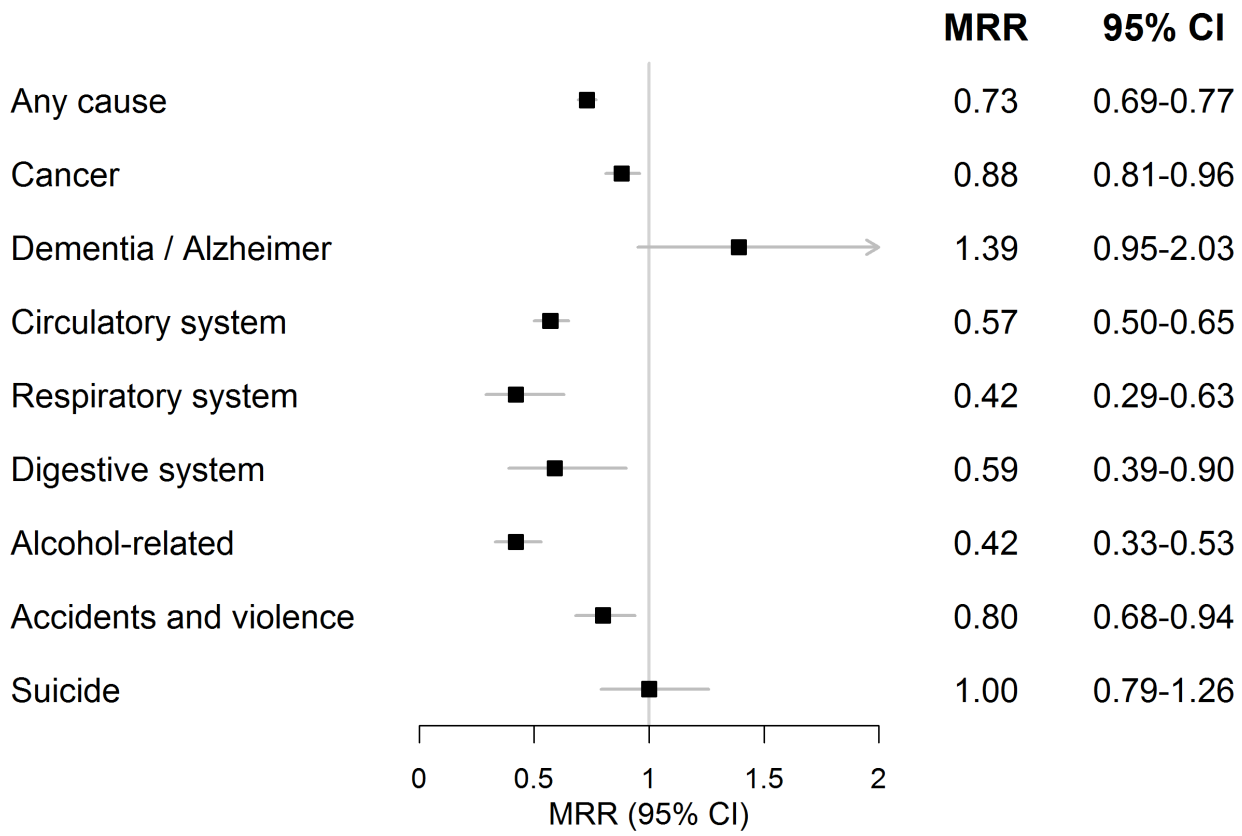

Figure II. Adjusted mortality rate ratios (MRR) and their 95% confidence intervals (CI) for any cause of death and for the certain death causes in the endometriosis cohort compared to the reference cohort.

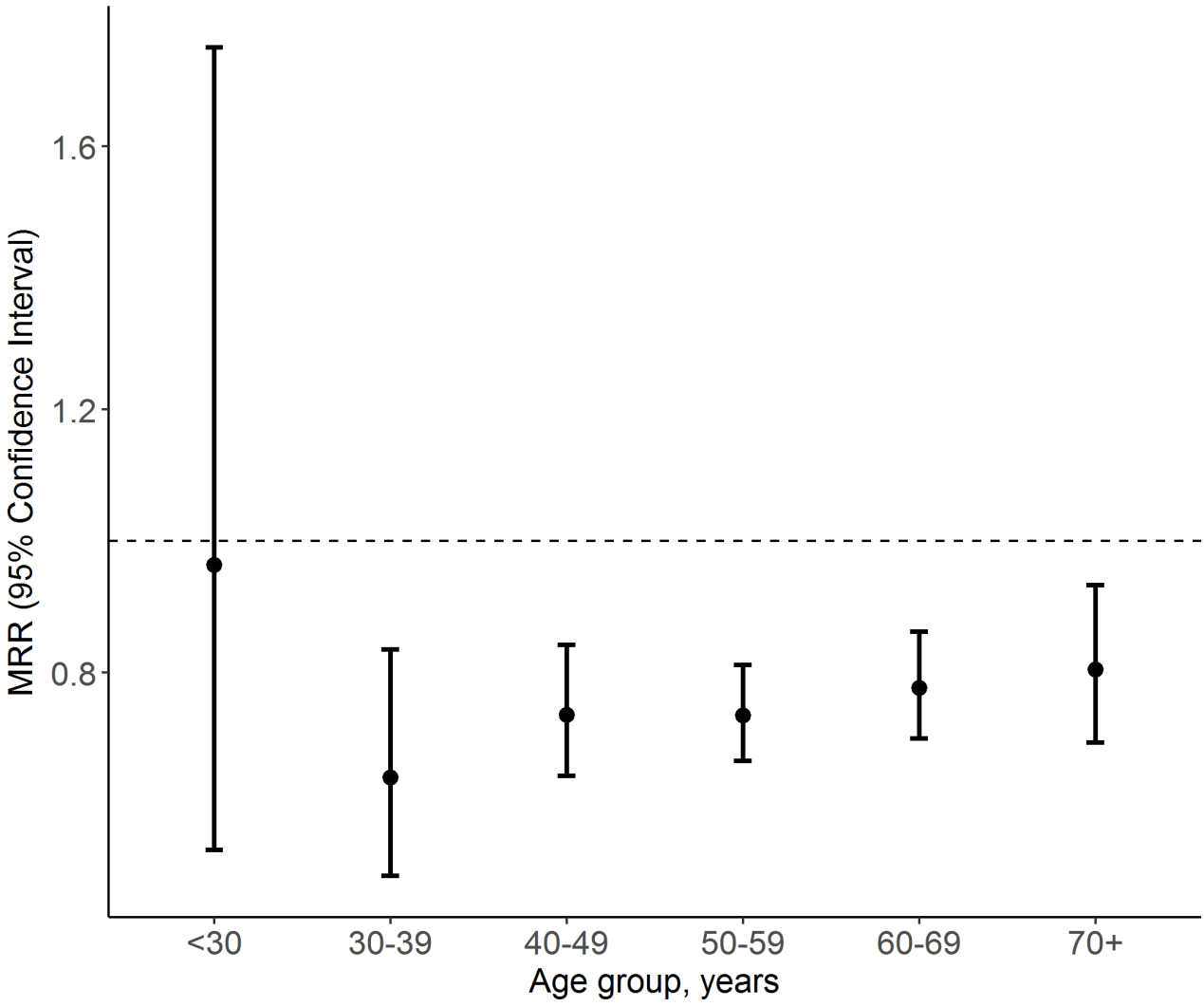

Figure III. The age-specific relative difference in all-cause mortality for the endometriosis cohort compared to the reference cohort.