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Excess mortality associated with eating disorders: a population-based cohort study.

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Keywords:	Anorexia Nervosa, Bulimia Nervosa, Eating Disorders NOS, Mortality, Epidemiology
Publishing Category:	Eating Disorders
Abstract:	Background Individuals with eating disorders (EDs) have a high mortality risk. Few population-based studies have estimated mortality risk in EDs other than anorexia nervosa. Aims To investigate all-cause mortality within a population-based cohort of individuals who received hospital-based care for any ED (anorexia nervosa, bulimia nervosa or ED not otherwise specified) in Ontario, Canada. Methods We conducted a retrospective-cohort study of 19,041 individuals with an ED from January 1, 1990, to December 31, 2013 using administrative healthcare data. The outcome of interest was death. Excess mortality was assessed using standardized mortality ratios (SMRs) and potential years of life lost (PYLL). Cox proportional hazards regression models were used to examine socio-demographic and medical comorbidities associated with greater mortality risk. Results The ED cohort had 17,108 females (89.9%) and 1,933 males (10.1%). The all-cause mortality for the entire ED cohort was five times higher than expected compared to the Ontario population (SMR = 5.06; 95% CI:4.82-5.30). SMRs were higher for males (SMR=7.24; 95% CI: 6.58-7.96) relative to females (SMR=4.59; 95% CI: 4.34-4.85), overall and in all age groups in the cohort. For both sexes, the ED cohort PYLL was more than 6 times higher than the expected PYLL in the Ontario population.

	Conclusions and Relevance Patients with EDs experience five to seven times higher mortality rates compared to the overall population. There is an urgent need to understand the mortality risk factors to improve health outcomes among individuals with eating disorders.

1 **Excess mortality associated with eating disorders: a population-based cohort study**
2
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11   **KEY POINTS**

12   **Question:** What is the mortality rate for individuals with eating disorders?

13   **Findings:** This study of 19,041 individuals with eating disorders found that eating disorders are

14   associated with an elevated risk of premature of death. The all-cause mortality for the entire cohort

15   was five times higher than expected compared to the general population. Standardised mortality ratios

16   were higher overall for males (SMR = 7.24) relative to females (SMR = 4.59).

17   **Meaning:** Individuals with eating disorders experience excess premature mortality compared to the

18   general population. These findings highlight the need to develop focused interventions for this group

19   to improve health outcomes.

20

2

ABSTRACT

Background

Individuals with eating disorders (EDs) have a high mortality risk. Few population-based studies have estimated mortality risk in EDs other than anorexia nervosa.

Aims

To investigate all-cause mortality within a population-based cohort of individuals who received hospital-based care for any ED (anorexia nervosa, bulimia nervosa or ED not otherwise specified) in Ontario, Canada.

Methods

We conducted a retrospective-cohort study of 19,041 individuals with an ED from January 1, 1990, to December 31, 2013 using administrative healthcare data. The outcome of interest was death. Excess mortality was assessed using standardized mortality ratios (SMRs) and potential years of life lost (PYLL). Cox proportional hazards regression models were used to examine socio-demographic and medical comorbidities associated with greater mortality risk.

Results

The ED cohort had 17,108 females (89.9%) and 1,933 males (10.1%). The all-cause mortality for the entire ED cohort was five times higher than expected compared to the Ontario population (SMR = 5.06; 95% CI:4.82-5.30). SMRs were higher for males (SMR=7.24; 95% CI: 6.58-7.96) relative to females (SMR=4.59; 95% CI: 4.34-4.85) overall, and in all age groups in the cohort. For both sexes, the ED cohort PYLL was more than 6 times higher than the expected PYLL in the Ontario population.

Conclusions and Relevance

Patients with EDs experience five to seven times higher mortality rates compared to the overall population. There is an urgent need to understand the mortality risk factors to improve health outcomes among individuals with eating disorders.

Declaration of Interest

None.

Keywords:

3

48   Eating disorders; anorexia nervosa; bulimia nervosa; EDNOS; mortality; standardized mortality ratio;
49   male; female
50

51   WORD COUNT: 3,270 (excludes abstract and key points)
52

53   **Relevance Statement**

54   Eating disorders, including anorexia nervosa, bulimia nervosa, and eating disorders not otherwise specified, are

55   associated with high illness burden, including mortality. This study uses population-based data to estimate

56   standardized mortality ratios (SMRs) comparing the rate of mortality amongst individuals with eating disorders

57   to the general population in Ontario, Canada. The SMR for individuals with eating disorders was 5.06, reflecting

58   a 5-fold increase in mortality risk for individuals with eating disorders. For males, the risk was 7-fold higher (SMR

59   - 7.24). Understanding the risk factors for the increased mortality in eating disorders is critical to reduce

60   mortality in this clinical population.

4

INTRODUCTION

Eating disorders are associated with a high risk of mortality and high illness burden including major depression, post-traumatic stress disorder, and chronic conditions including cardiovascular, heart failure, musculoskeletal and renal complications as observed in clinical population samples. (1-4) One meta-analysis reported an overall elevated mortality rate for eating disorders (anorexia nervosa, bulimia nervosa, and eating disorder not otherwise specified), which in some instances was much higher than other psychiatric disorders. (5) Eating disorders have also been associated with high health care costs, related to both psychiatric and non-psychiatric hospitalizations. Previous research has found that direct health care costs for individuals hospitalised for an eating disorder were about $48 million, with higher costs for those under the age of 20 and those 65 and older. (1) However, few population-based surveillance studies estimating incidence, prevalence and mortality in eating disorders have been published (2, 6, 7), with the literature on the epidemiology and outcomes of eating disorders having significant limitations such as small sample sizes and few large-scale mental health surveillance studies.(2, 6)

Most of the literature reporting on mortality in eating disorder patients comes from studies examining cohorts in specific treatment settings, which are difficult to compare given the wide variability in treatment target populations, insurance coverage and other selection biases. (8, 9) Several mortality studies report only crude case fatality rates (i.e., they report on deaths among patients with no comparison group or adjustment for expected mortality in the same age population); other studies are limited in sample size or scope and report only on anorexia nervosa and/or only examine female patients.(9, 10) Eating disorders have been misperceived as rare perhaps due to limited awareness of the available data on the burden of disease or a misconception that only the most

83   severe cases experience a severe burden. (11, 12) Furthermore, the lack of comprehensive data on

84   eating disorders that includes both males and females has made it difficult to estimate all-cause and

85   cause-specific mortality among this population.

86   This study describes all-cause mortality rates within a population-based cohort of patients with

87   an eating disorder in a context of universal public health care funding. Excess mortality among these

88   patients was estimated relative to the general population without an eating disorder using

89   standardized mortality ratios (SMRs) and potential years of life lost (PYLL) (in total and attributable to

90   eating disorders). In addition, factors associated with increased hazard of mortality within the ED

91   cohort were examined including patient socio-demographic and comorbidity measures as well as

92   indicators of health care service utilization.

93

94   **METHODS**

95   **Study design**

96   This study examines a population-based, retrospective cohort of individuals who received care

97   for an eating disorder in any hospital in Ontario from January 1, 1990, to December 31, 2013. The

98   cohort was followed, through record-linkage, until date of death or December 31, 2013, the latest date

99   possible based on data availability at the time of the analysis).

100   **Data sources**

101   We made use of administrative health care data available through ICES in Toronto, Ontario.

102   ICES is an independent non-profit organization funded by the Ontario Ministry of Health and holds an

103   inventory of coded and linkable health datasets, encompassing much of the publicly funded

104   administrative health services records for the Ontario population eligible for universal health coverage

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105 since 1986. This data repository includes individual-level, linkable longitudinal data on most publicly

106 funded health care services. The Registered Persons Database (RPDB), a population-based registry,

107 contains anonymized demographic data on all insured members of the universal Ontario Health

108 Insurance Plan (OHIP), such as sex, date of birth, urban or rural dwelling information and

109 neighbourhood-level income (measured in quintiles at the census tract level). Information on date and

110 cause of death (where applicable) were obtained from the Ontario Registry General-Death Vital

111 Statistics. Hospital admissions and associated diagnostic codes used to define the cohort were

112 obtained from the following health care administrative databases maintained by the Canadian Institute

113 for Health Information: Discharge Abstract Database (DAD) for non-mental health admissions and

114 National Ambulatory Care Reporting System (NACRS) for emergency department visits. Psychiatric

115 hospitalization records were obtained from the Ontario Mental Health Reporting System (OMHRS)

116 database.

117   Co-morbidity data for chronic medical conditions were obtained via the following validated

118 patient cohorts and registries developed, linked and analyzed at ICES including: Ontario Congestive

119 Heart Failure (CHF) Database; Chronic Obstructive Pulmonary Disease (COPD) Database; Ontario

120 Diabetes Database (ODD); Ontario Asthma Database; Ontario HIV Database and Ontario Cancer

121 Registry (OCR). These datasets have been described elsewhere. (13)

122 **Derivation of the eating disorder patient cohort**

123   Individuals were included if they received an eating disorder diagnosis during an emergency

124 department visit, medical hospitalization, or psychiatric hospitalization from 1990 to 2013. The first

125 diagnosis from any of these data sources was determined as the cohort entry date. Cohort

126 development and analyses were carried out with linked administrative health care data holdings at

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127   ICES. Diagnostic codes used to identify eating disorder patients included: ICD-9 codes 307.1 (anorexia

128   nervosa), 307.51 (bulimia nervosa), 307.50 (eating disorders not otherwise specified); ICD-10 codes

129   F50.0 (eating disorders), F50.1 (anorexia nervosa), F50.2, F50.3 (bulimia nervosa), F50.8, F50.9

130   (EDNOS), and DSM-IV codes 307.1 (anorexia nervosa), 307.51 (bulimia nervosa), 307.50 (EDNOS). We

131   restricted our study to these three ED diagnoses because the publicly-funded services in Ontario focus

132   on the treatment of these ED diagnoses. ED diagnosis codes do not apply to children under the age of

133   5. Furthermore, children ages 5 to 9 were excluded as the small number of deaths precluded reporting

134   under Ontario privacy regulations. We excluded individuals who ceased to be publicly insured for

135   health care at date of cohort entry. This approach resulted in a cohort of 19,041 individuals with and

136   eating disorder diagnosis (including all patients deceased or alive to the end of December 31, 2013).

137   The development of this cohort, restricted to individuals alive as of January 1,2014, has also

138   been described elsewhere. (14)

139   **Analysis**

140   Mortality rates were estimated for the full cohort and were reported as deaths per 1,000

141   person-years of observation time, overall and by sex (female and male), calendar year (from 1990 to

142   2013), and age groups. Person-years of follow-up were segregated by sex, calendar year and age

143   attained over follow-up (to end of follow-up, or death) for each cohort member. This was achieved

144   using Lexis expansion tools for cohort data using Stata 14 (StataCorp. 2015. *Stata Statistical Software:*

145   *Release 14*. College Station, TX: StataCorp LP). Excess mortality in the eating disorder population,

146   relative to the underlying Ontario population, was illustrated in several ways including SMRs, PYLL in

147   the cohort, and proportion of PYLL attributable to eating disorder.

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148   SMRs were estimated using the indirect method.(15) SMRs were defined as the number of

149   observed deaths in the eating disorder cohort divided by the number of expected deaths in the cohort

150   if the eating disorder cohort had had the same sex- and age-specific mortality experience as the

151   underlying Ontario population. Expected mortality rates in the general population were obtained

152   using all Ontario deaths in 2011 and corresponding data for the 2011 Census year. SMRs were

153   presented with exact Poisson-based 95% confidence intervals.

154   Person Years of Life Lost (PYLL) within the eating disorder cohort were estimated as the sum of

155   all years of life lost before age 75 (16) for observed deaths among patients with an eating disorder

156   (expressed as PYLL per 1,000 persons). Expected and excess (eating disorder attributable) PYLL values

157   were also estimated using expected deaths from Ontario 2011 standard mortality rates. The

158   theoretical percent of total PYLL attributable to being in the eating disorder cohort (relative to the

159   underlying population) was defined as attributable PYLL = (total cohort PYLL – expected PYLL)/ total

160   cohort PYLL and expressed as a percentage.

161   Socio-demographic factors associated with higher risk of mortality within the cohort were

162   examined using Cox Proportional Hazard regression models for all-cause mortality.   Patients who

163   entered the cohort with an eating disorder diagnosis on the same day as death contributed no follow-

164   up time and were excluded from the survival models (N=5). Separate Cox models were estimated for

165   patients aged 10 to 44 at entry and those 45 and older. Patient socio-demographic characteristics

166   considered were age, sex and calendar year over the period of the study, as well as neighbourhood-

167   level household income quintile and rurality of residence. Models examining the effect of socio-

168   demographic variables were then further adjusted for medical co-morbidity (i.e., chronic conditions,

169   defined beforehand). The adjusted models included six chronic conditions derived from validated

170   cohorts through administrative databases.

171   Model diagnostics were performed and indicated no violations of assumptions. This included

172   confirmation of the validity of a linear effect of age as a continuous covariate in the exponential Cox

173   model, assessment for non-violation of the assumption of proportional hazards, and lack of excess

174   multi-collinearity.

175   **Ethics and approvals**

176   ICES is an independent, non-profit research institute whose legal status under Ontario's health

177   information privacy law allows it to collect and analyze health care and demographic data, without

178   consent, for health system evaluation and improvement. Thus, the use of data in this project was

179   authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not

180   require review by a Research Ethics Board.   The project was approved by the Research Ethics Board at

181   University Health Network, Toronto.

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183   **RESULTS**

184   Baseline characteristics of the eating disorder cohort are presented in Table 1. Of the 19,041

185   cohort members, 17,108 were female (89.9%) and 1,933 were male (10.1%). Age at cohort entry

186   ranged from 10 to over 85 years of age, but 88.9% of the population entered the cohort between the

187   ages of 14 and 44. Most of the cohort (88.8%) resided in urban centres. A greater percentage of the

188   cohort lived in middle to low-income neighbourhoods, with 37.4% in the lowest neighbourhood level

189   income category and 18.0% in the middle-income neighbourhood level income category. Categories for

190   eating disorder-specific diagnoses at cohort entry revealed multiple diagnoses for the same individual

191   over time; 31.8% of the cohort had anorexia nervosa alone or in combination with bulimia nervosa

192   and/or eating disorder not otherwise specified (EDNOS); 35.1% of the cohort had a diagnosis of EDNOS

193   alone at enrolment. Eating disorder diagnoses were also comorbid with other medical conditions

194   including asthma (27.0%), diabetes (8.9%), cancer (4.6%) and congestive heart failure (3.5%).

195   Table 2 presents descriptive statistics for the mortality follow-up analysis of this cohort,

196   including total person-years of follow up and observed deaths, for the whole cohort and by age group

197   and sex. Mortality rates and SMRs by age group and sex are also presented in Table 2. For the entire

198   eating disorder cohort and across all age groups, the all-cause mortality rate was five times higher than

199   expected based on mortality rates in the Ontario population (marginal SMR = 5.06; 95% CI:4.82-5.30).

200   Peak values for SMRs were observed among adults from approximately 30 to 44 years of age.

201   Mortality rates and SMRs were unstable for individuals 10 to 14 due to small number of deaths. SMRs

202   were higher for male eating disorder patients, relative to female, overall and in all age groups. For

203   females, the marginal SMR was 4.59 (95% CI: 4.34-4.85) while for males it was 7.24 (95% CI: 6.58-7.96).

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204   Excess mortality is further illustrated in Figure 1, which presents cohort and population mortality rates

205   (per 1,000 population) by age and sex as well as age-sex specific SMRs.

206   The overall expected PYLL (based on expected numbers of deaths in the cohort using the 2011

207   Ontario age-specific death rates) was estimated at 29.54 years per 1,000 population (95% CI: 28.7-

208   30.4) and similar for each sex separately (Appendix Table 1). Within the eating disorder cohort,

209   estimated total PYLL before age 75 equalled 191.6 per 1,000 population (95% CI: 189.4-193.8), for

210   both sexes, combined. Years of life lost per 1,000 population was higher for males (PYLL within

211   cohort=375.6; 95% CI: 364.7-386.8) relative to females (PYLL within cohort=174.1; 95% CI: 171.9-

212   176.3). For both sexes, the excess PYLL attributable to experiencing an eating disorder was 84%. For

213   female eating disorder patients, it was estimated that 83% of PYLL were attributable to being in the

214   eating disorder cohort; for male eating disorder patients, this value was 92%. Among all Ontario ED

215   patients, over the period of this study, it was estimated that 24,773 years of life were lost due to eating

216   disorder, before the age of 75.

217   Cox survival models on all-cause mortality, controlling for the effects of demographic

218   characteristics, appear in Table 3. For both age groups (10-44 and >=45 years of age), older age (as a

219   continuous, linear term) and male sex were associated with statistically significant increased mortality

220   risk and adjusted hazard ratio of 1.91 in both age groups. Additionally, mortality declined over

221   calendar years in the analysis showing a statistically significant effect of calendar year on the

222   downward trend in mortality over time (adjusted hazard ratio of 0.9, year over year). In addition, the

223   pattern of association with household income quintile was not a simple linear association, but rather a

224   U-shaped pattern. Higher total mortality hazard ratios were observed in the highest and lowest

225   income quintiles, relative to household income quintiles in the middle.

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226   Fully adjusted models for age, sex and calendar year resulted in opposite findings for rurality in

227   the analyses for cohort members under and over 45 years of age. Rural residence was associated with

228   lower mortality for cohort members under the age of 45 but higher mortality risk for cohort members

229   45 or older. Control variables for non-ED chronic medical conditions (CHF, COPD, cancer and HIV) were

230   all positively associated with higher mortality ratios with the exceptions of inverse associations for

231   asthma and diabetes diagnoses within cohort members age 45 and over. For cohort members ages 44

232   and younger, having a diagnosis of CHF, cancer, diabetes and HIV was positively associated with higher

233   mortality ratios. We observed a simple linear trend toward lower mortality with calendar year of entry

234   into the cohort. This cannot be separated from a general trend in improved survival in the population

235   as age-sex specific mortality risk expected in the population are not updated for each calendar year but

236   based on census years (here based on the 2011 Canadian census).

237

238   **DISCUSSION**

239   The purpose of this study was to estimate the excess mortality and burden associated with

240   eating disorders using comprehensive population-based data. Notably, this study is among the few

241   internationally that have made use of a population-based eating disorder cohort and to have provided

242   SMR estimates specific to both female and male patients. Our findings show that individuals with

243   eating disorders diagnosed in hospital settings had a mortality rate of approximately 5-fold higher than

244   the general population, with more than 80% of life lost before the age of 75 for females and males.

245   In female eating disorder patients, we found a roughly five-fold mortality rate relative to the

246   general population. This is similar in magnitude to what has been reported in two international meta-

247   analyses (5, 8) and similar in magnitude to SMRs reported specifically for anorexia nervosa (anorexia

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248   nervosa being the eating disorder diagnosis with the highest SMRs). Whilst studies have reported on

249   the lifetime prevalence of eating disorders in males ranging from 0.1 to 2.0 for all types,(2, 9) few

250   studies have reported on the mortality rates among males with eating disorders and those studies tend

251   to report exclusively on anorexia nervosa.(17, 18) Our study thus makes a novel and important

252   contribution to the sparse literature on male eating disorder patients and their mortality experience,

253   with a substantially larger sample of male eating disorder patients.

254   The SMRs observed in males were almost 2-fold higher than in females. This observation of

255   higher mortality in males with eating disorders is particularly concerning as there is evidence to

256   suggest that males are less likely to self-identify or be identified with eating disorders unless the illness

257   severity is are extremely high. Additionally, eating disorder treatment centres are less likely to accept

258   male patients (19, 20). Gender and cultural differences in help-seeking behaviours in male eating

259   disorder patient may result in services being less accessible, contributing to worse outcomes. This

260   highlights the need for enhanced case-identification, research and services for male eating disorder

261   patients to improve outcomes (21). We also found that mortality risk was higher amongst younger

262   individuals within the cohort and individuals living in the lowest income neighbourhoods, highlighting

263   issues related to equity of access and quality of care; this warrants further investigation.

264   While there have been two meta-analyses estimating ED-related mortality, (5, 8) the existing

265   literature has methodological issues including a lack of population-based surveillance data (limited to

266   sub-regional studies and registries from restricted clinical practices(3, 22)), selection of study

267   population, identification of cases, and small sample size.(9, 10, 17, 23-25)

268   Finally, our results demonstrate the degree to which patients with EDs also experience

269   important medical conditions and co-morbidities, such as congestive heart failure, diabetes, COPD and

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270 hypertension amongst others. Mechanisms through which EDs may have a causal impact on diverse

271 chronic diseases have been described elsewhere. (4)

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273 **STRENGTHS AND LIMITATIONS**

274   A major strength of our study was the use of a population-based sample, which is more

275 representative and generalizable than cohorts based on a sample of hospitalised patients from

276 individual treatment centres or insurance programs. An additional methodological strength was the

277 use of the recommended SMR method, which is replicable and well established, to report excess

278 mortality relative to the underlying population as well as controlling for sex and age through

279 standardization (as opposed to merely reporting case-fatality rates within the clinical cohort).

280   One major limitation is the lack of validation of our algorithm for case-detection, which relied

281 on hospital contact data and not outpatient contact data. This may bias towards higher severity of

282 cases and may also truncate the time between illness identification and mortality, which could result in

283 an overestimation of mortality rates.(26) These are limitations of all research involving clinical cohorts

284 based on administrative or insured services data. These inherent limitations of the best data available

285 underscore how important it is to have disease registries for eating disorders established

286 internationally, with high quality clinical measures, which are available only in localized clinical

287 research cohorts (22). Moreover, the lack of data on ethnicity did not allow us to produce ethnic-

288 specific SMRs; future research should seek to address this limitation. Finally, this study included a

289 specific group of ED diagnoses (anorexia nervosa, bulimia nervosa, and ED NOS) for which treatment is

290 available in Ontario's publicly funded system. We did not include other eating disorder diagnoses such

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291   as binge-eating disorder, and it is unclear whether the findings from our study would generalize to a

292   broader array of eating disorder diagnoses.

293

294   **IMPACT AND RELEVANCE**

295   In summary, our study provides evidence of the high mortality rate associated with eating

296   disorder diagnoses. Furthermore, males with eating disorders have a higher risk of mortality than

297   females, which underscores the importance of detecting and treating eating disorders in males even

298   though they are relatively low in prevalence. These findings are consistent with previous research on

299   excess mortality; we effectively show the marked gender differences in risk of mortality and actual

300   excess mortality in the eating disorder population. Historically, the burden of eating disorders,

301   including mortality, has been documented to a lesser extent compared to studies of other psychiatric

302   conditions despite its prevalence and high mortality rate.

303   This study serves to highlight the need for ongoing population-based surveillance of eating

304   disorder burden. Early intervention in eating disorders is known to be effective (27) (28) and presents

305   an opportunity to reduce the mortality impact (high and early onset mortality) of these conditions. The

306   inclusion of eating disorders amongst other disorders identified as high priority for improved

307   surveillance and burden of disease data in mental health also highlights a need for better detection of

308   and treatment of eating disorders and associated psychiatric comorbidities to improve long-term

309   outcomes.

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326 **Author Contribution**

331 **Data Availability**

332   The dataset from this study is held securely in coded form at ICES. While data sharing

333   agreements prohibit ICES from making the dataset publicly available, access may be granted to those

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334   who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full

335   dataset creation plan and underlying analytic code are available upon request, understanding that the

336   computer programs may rely upon coding templates or macros that are unique to ICES and are

337   therefore either inaccessible or may require modification.

338   **Declaration of Interest:** None

339

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405   Tables and Figures

406   Table 1: Demographic and Clinical Characteristics of the Eating Disorder cohort

VARIABLE	Female	Male	TOTAL	P-VALUE Sex differences (unadjusted)
	N=17,108	N=1,933	N=19,041	
Age at first diagnosis, *Mean ± SD*	*25.76 ± 15.44*	*37.37 ± 23.91*	*26.94 ± 16.87*	<0.001
	N (% of cohort, females)	N (% of cohort, males)	N (% of cohort)	
Age group at diagnosis				
10_13	1,359 (7.9)	197 (10.2)	1,556 (8.2)	
14_17	5,613 (32.8)	370 (19.1)	5,983 (31.4)	
18_24	4,015 (23.5)	279 (14.4)	4,294 (22.6)	
25_44	4,231 (24.7)	443 (22.9)	4,674 (24.5)	
45_64	1,201 (7.0)	279 (14.4)	1,480 (7.8)	
65_84	519 (3.0)	290 (15.0)	809 (4.2)	
>=85	170 (1.0)	75 (3.9)	245 (1.3)	
Neighbourhood Income Quintile				
1 (low)	3,164 (18.5)	434 (22.5)	3,598 (18.9)	<0.001
2 (medium-low)	3,149 (18.4)	366 (18.9)	3,515 (18.5)	
3 (medium)	3,143 (18.4)	365 (18.9)	3,508 (18.4)	
4 (medium-high)	3,460 (20.2)	377 (19.5)	3,837 (20.2)	
5 (high)	4,105 (24.0)	374 (19.3)	4,479 (23.5)	
Missing	87 (0.5)	17 (0.9)	104 (0.5)	
Rural residence				
No	15,186 (88.8)	1,710 (88.5)	16,896 (88.7)	0.691
Yes	1,922 (11.2)	223 (11.5)	2,145 (11.3)	
Clinical Characteristics				
Eating Disorder Diagnosis at cohort entry				
AN and BN	121 (0.7)	7 (0.4)	128 (0.7)	<0.001
AN and EDNOS	*	*	55 (*)	
AN only	5,437 (31.8)	398 (20.6)	5,835 (30.6)	
AN, BN, and EDNOS	291 (1.7)	7 (0.4)	298 (1.6)	
BN and EDNOS	2,981 (17.4)	353 (18.3)	3,334 (17.5)	
BN only	2,218 (13.0)	137 (7.1)	2,355 (12.4)	
EDNOS only	6,008 (35.1)	1,028 (53.2)	7,036 (37.0)	
Co-morbidity				
Asthma	4,759 (27.8)	480 (24.8)	5,239 (27.5)	0.005
Cancer	638 (3.7)	225 (11.6)	863 (4.5)	<0.001
COPD	1,237 (7.2)	300 (15.5)	1,537 (8.1)	<0.001

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Congestive Heart Failure	472 (2.8)	190 (9.8)	662 (3.5)	<0.001
Diabetes	1,390 (8.1)	343 (17.7)	1,733 (9.1)	<0.001
HIV	23 (0.1)	22 (1.1)	45 (0.2)	<0.001

407 **Legend:** SD-standard deviation; AN-Anorexia Nervosa; BN-Bulimia Nervosa; EDNOS-Eating Disorder Not Otherwise
408 Specified; COPD- Chronic Obstructive Pulmonary Disease; HIV, Human Immuno-Deficiency Virus
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411   Table 2 All-cause mortality comparing the ED cohort to the Ontario population overall and by sex. *

Age group	Person Years (in 1000's)	Observed deaths	Expected deaths	Crude mortality rates (per1,000)	SMR* (per 1000)(95% CI)
Both Sexes					
Overall	155,921.03	1672	330.85	10.88	5.1 (4.8-5.3)
15-19	22,842.62	32	6.72	1.42	4.8 (3.3-6.7)
20-24	29,121.61	59	11.57	2.04	5.1 (4.0-6.6)
25-29	25,621.18	68	10.22	2.66	6.7 (5.3-8.4)
30-34	20,068.30	84	12.04	4.19	7.0 (5.6-8.6)
35-39	14,937.13	92	10.46	6.16	8.8 (7.2-10.8)
40-44	11,810.93	107	12.99	9.06	8.2 (6.8-10.0)
45-49	9,362.66	126	16.85	13.46	7.5 (6.3-8.9)
50-54	6,407.25	116	19.86	18.10	5.8 (4.9-7.0)
55-59	3,871.77	90	18.58	23.25	4.8 (3.9-6.0)
60-64	2,232.77	83	16.3	37.17	5.1 (4.1-6.3)
65-69	1,331.44	105	15.44	78.86	6.8 (5.6-8.2)
70-74	1,012.38	113	18.53	111.62	6.1 (5.1-7.3)
75-79	875.12	137	26.78	156.55	5.1 (4.3-6.1)
80-84	765.24	180	40.25	235.22	4.5 (3.9-5.2)
85-89	474.79	172	42.87	362.26	4.0 (3.5-4.7)
90+	292.76	104	51.06	355.24	2.0 (1.7-2.5)
Female					
Overall	142,655.30	1249	272.29	8.83	4.6 (4.3-4.9)
15-19	20980.86	25	6.21	1.20	4.0 (2.7-6.0)
20-24	27195.17	50	10.83	1.85	4.6 (3.5-6.1)
25-29	24203.29	61	9.66	2.53	6.3 (4.9-8.1)
30-34	18855.12	71	11.31	3.77	6.3 (5.0-7.9)
35-39	13822.51	80	9.68	5.79	8.3 (6.6-10.3)
40-44	10747.7	90	11.82	8.37	7.6 (6.2 -9.4)
45-49	8479.574	106	15.26	12.50	7.0 (5.7-8.4)
50-54	5761.355	94	17.86	16.32	5.3 (4.3-6.4)
55-59	3433.343	73	16.48	21.26	4.4 (3.5-5.6)
60-64	1861.803	61	13.59	32.76	4.5 (3.5-5.8)
65-69	1048.189	70	12.16	66.78	5.8 (4.6-7.3)
70-74	755.4538	67	13.82	88.69	4.9 (3.8-6.2)
75-79	653.2047	85	19.99	130.13	4.3 (3.4-5.3)
80-84	583.2382	114	30.68	195.46	3.7 (3.1-4.5)
85-89	348.6016	119	31.48	341.36	3.8 (3.2-4.5)
90+	236.0726	80	41.17	338.88	1.9 (1.6-2.4)
Male					

Overall	1,213.18	423	58.56	34.56	7.2 (6.6-8.0)
15-19	1861.75	7	0.5	4.17	13.9 (6.6-29.2)
20-24	1926.44	9	0.74	4.85	12.1 (6.3-23.3)
25-29	1417.89	7	0.56	5.00	12.5 (6.0-26.2)
30-34	1213.182	13	0.73	10.72	17.9 (10.4-30.8)
35-39	1114.625	12	0.78	10.77	15.4 (8.7-27.1)
40-44	1063.231	17	1.17	15.99	14.5 (9.0-23.4)
45-49	883.0904	20	1.59	22.65	12.6 (8.1-19.5)
50-54	645.8871	22	2	34.06	11.0 (7.2-16.7)
55-59	438.4278	17	2.1	38.77	8.1 (5.0-13.0)
60-64	370.974	22	2.71	59.30	8.1 (5.4-12.3)
65-69	283.245	35	3.29	123.57	10.7 (7.7-14.8)
70-74	256.9281	46	4.7	179.04	9.8 (7.3-13.1)
75-79	221.9124	52	6.79	234.33	7.7 (5.8-10.1)
80-84	182.0007	66	9.57	362.64	6.9 (5.4-8.8)
85-89	126.1937	53	11.4	419.99	4.7 (3.6-6.1)
90+	56.68994	24	9.89	423.36	2.4 (1.6-3.6)

412 *SMRs are stratified by age-group where age is a time-dependent covariate reflecting age attained during follow-up as
413 opposed to at baseline. Time-dependent age calculated using STATA command STSPLIT.
414 **Legend:** SMR - standardized mortality ratio; CI – confidence interval

415 Table 3 Predictors of relative excess mortality from Cox survival models for all-cause mortality within eating
416 disordered cohort.

	Unadjusted Hazard Ratio	95% Confidence Interval	Adjusted Hazard Ratio	Hazard Ratio 95% Confidence Interval	P-value* (degrees of freedom)
Age 10 to 44- N=16,507					
Age** (integer, continuous)	1.07	(1.06 – 1.07)	1.05	(1.05 – 1.06)	< 0.001 (1)
Calendar year (integer, continuous)	0.90	(0.89 – 0.90)	0.91	(0.91 – 0.92)	< 0.001 (1)
Sex (male versus female)	2.06	(1.92 – 2.21)	1.91	(1.78 – 2.05)	< 0.001 (1)
Neighbourhood income quintile					
1 (low)	1.36	(1.27 – 1.46)	1.26	(1.18 – 1.35)	< 0.001 (4)
2 (medium-low)	0.83	(0.76 – 0.89)	0.81	(0.75 – 0.87)	< 0.001 (4)
3 (medium)	0.95	(0.88 – 1.01)	0.97	(0.89 –1.04)	0.39 (4)
4 (medium-high)	0.96	(0.89 – 1.03)	0.98	(0.91 –1.05)	0.54 (4)
5 (high)			1.00	Reference-	
Rural residence (versus urban residence)	0.65	(0.60 – 0.71)	0.69	(0.63 - 0.75)	< 0.001 (1)
Medical co-morbidity indicators (binary):					
Congestive heart failure			2.45	(2.23 – 2.69)	< 0.001 (1)
COPD			1.07	(0.99 – 1.14)	0.07 (1)
Cancer			2.43	(2.25 – 2.62)	< 0.001 (1)
Asthma			1.01	(0.96 – 1.06)	0.76 (1)
Diabetes			1.75	(1.65 – 1.86)	< 0.001 (1)
HIV			2.16	(1.75 – 2.67)	< 0.001 (1)
Age 45 and older- N=2532					
Age** (integer, continuous)	1.08	(1.08 – 1.08)	1.07	(1.07 – 1.08)	< 0.001 (1)
Calendar year (integer, continuous)	0.88	(0.87 – 0.88)	0.89	(0.88 – 0.89)	< 0.001 (1)
Sex (male versus female)	1.92	(1.82 – 2.01)	1.91	(1.82 – 2.02)	< 0.001 (1)
Neighbourhood income quintile:					
1 (low)	1.47	(1.37 – 1.56)	1.33	(1.25 – 1.42)	< 0.001 (4)
2 (medium-low)	1.11	(1.04 – 1.19)	1.01	(0.94 – 1.08)	0.86 (4)
3 (medium)	1.04	(0.97 – 1.11)	0.93	(0.86 – 0.99)	0.04 (4)
4 (medium-high)	0.85	(0.79 – 0.91)	0.79	(0.74 – 0.85)	< 0.001 (4)
5 (high)			1.00	Reference-	
Rural residence (versus urban residence)	1.27	(1.19 – 1.35)	1.22	(1.15 – 1.30)	< 0.001 (1)
Medical co-morbidity indicators (binary):					
Congestive heart failure			1.32	(1.25 – 1.38)	< 0.001 (1)
COPD			1.06	(1.01 – 1.11)	< 0.03 (1)
Cancer			2.24	(2.14 – 2.35)	< 0.001 (1)
Asthma			0.94	(0.89 – 0.99)	0.03 (1)
Diabetes			0.89	(0.86 – 0.94)	< 0.001 (1)
HIV			2.06	(1.59 – 2.66)	< 0.001 (1)

417 * Likelihood ratio test for removal of covariate from fully adjusted model shown.
418 ** Age is defined as time-dependent covariate, meaning age of cohort member attained over follow-up and not at baseline.
419 Time-dependent age is calculated using STATA command STSPLIT.
420 **Legend**: COPD- Chronic Obstructive Pulmonary Disease; HIV, Human Immuno-Deficiency Virus
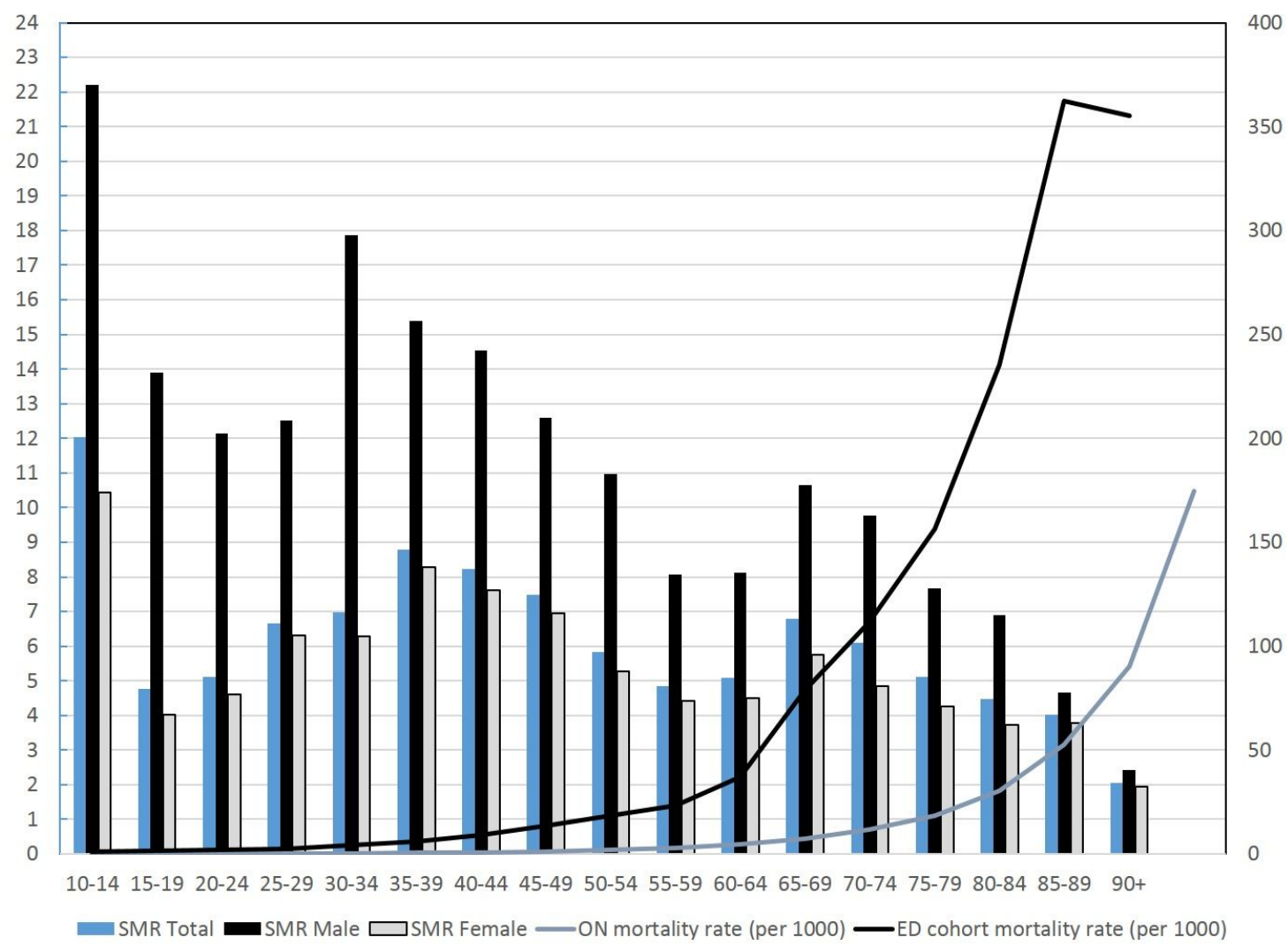421

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422 Appendix Table 1: Age-Sex matched person years of life lost and 95% CI in ED cohort and Ontario population in
423 2011

	ED Cohort PYLL (95% CI)	Ontario Population PYLL (95% CI)	Excess PYLL (%)
Both Sexes	191.5 (189.3-193.7)	29.6 (28.8-30.5)	85%
Male	375.4 (364.4-386.6)	29.6 (28.7-30.5)	92%
Female	174.8 (172.6-177.0)	29.7 (26.6-32.7)	83%

424
425 **Legend:** ED – eating disorders; CI – confidence interval; PYLL – Person Years of Life Lost
426

Figure 1: Standardized mortality ratios-by sex and age-group, all-cause mortality rates observed within the eating disorders cohort (1991-2013) and Ontario (2011) mortality rates

Y1 axis label (left)   Standardized Mortality Ratio (SMR)
Y2 axis label (right)   Observed morality rate (per 1000 person years)

28

Excess mortality associated with eating disorders: a population-based cohort study

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KEY POINTS

Question: What is the mortality rate for individuals with eating disorders?

Findings: This study of 19,041 individuals with eating disorders found that eating disorders are associated with an elevated risk of premature of death. The all-cause mortality for the entire cohort was five times higher than expected compared to the general population. Standardised mortality ratios were higher overall for males (SMR = 7.24) relative to females (SMR = 4.59).

Meaning: Individuals with eating disorders experience excess premature mortality compared to the general population. These findings highlight the need to develop focused interventions for this group to improve health outcomes.

2

ABSTRACT

Background

Individuals with eating disorders (EDs) have a high mortality risk. Few population-based studies have estimated mortality risk in EDs other than anorexia nervosa.

Aims

To investigate all-cause mortality within a population-based cohort of individuals who received hospital-based care for any ED (anorexia nervosa, bulimia nervosa or ED not otherwise specified) in Ontario, Canada.

Methods

We conducted a retrospective-cohort study of 19,041 individuals with an ED from January 1, 1990, to December 31, 2013 using administrative healthcare data. The outcome of interest was death. Excess mortality was assessed using standardized mortality ratios (SMRs) and potential years of life lost (PYLL). Cox proportional hazards regression models were used to examine socio-demographic and medical comorbidities associated with greater mortality risk.

Results

The ED cohort had 17,108 females (89.9%) and 1,933 males (10.1%). The all-cause mortality for the entire ED cohort was five times higher than expected compared to the Ontario population (SMR = 5.06; 95% CI:4.82-5.30). SMRs were higher for males (SMR=7.24; 95% CI: 6.58-7.96) relative to females (SMR=4.59; 95% CI: 4.34-4.85), overall, and in all age groups in the cohort. For both sexes, the ED cohort PYLL was more than 6 times higher than the expected PYLL in the Ontario population.

Conclusions and Relevance

Patients with EDs experience five to seven times higher mortality rates compared to the overall population. There is an urgent need to understand the mortality risk factors to improve health outcomes among individuals with eating disorders.

Declaration of Interest

None.

Keywords:

Eating disorders; anorexia nervosa; bulimia nervosa; EDNOS; mortality; standardized mortality ratio; male; female

WORD COUNT: 3,~~519~~ 270 (excludes abstract and key points)

Relevance Statement

Eating disorders, including anorexia nervosa, bulimia nervosa, and eating disorders not otherwise specified, are associated with high illness burden, including mortality. This study uses population-based data to estimate standardized mortality ratios (SMRs) comparing the rate of mortality amongst individuals with eating disorders to the general population in Ontario, Canada. The SMR for individuals with eating disorders was 5.06, reflecting a 5-fold increase in mortality risk for individuals with eating disorders. For males, the risk was 7-fold higher (SMR - 7.24). Understanding the risk factors for the increased mortality in eating disorders is critical to reduce mortality in this clinical population.

INTRODUCTION

Eating disorders are associated with a high risk of mortality and high illness burden including major depression, post-traumatic stress disorder, and chronic conditions including cardiovascular, heart failure, musculoskeletal and renal complications as observed in clinical population samples. (1-4) One meta-analysis reported an overall elevated mortality rate for ~~all~~ eating disorders (anorexia nervosa, bulimia nervosa, and eating disorder not otherwise specified)~~types~~, which in some instances was~~ere~~ much higher than other psychiatric disorders. (5) Eating disorders have also been associated with high health care costs, related to both psychiatric and non-psychiatric hospitalizations. Previous research has found that direct health care costs for individuals hospitalised for an eating disorder were about $48 million, with higher costs for those under the age of 20 and those 65 and older. (1) However, few population-based surveillance studies estimating incidence, prevalence and mortality in eating disorders have been published (2, 6, 7), with the literature on the epidemiology and outcomes of eating disorders having significant limitations such as small sample sizes and few large-scale mental health surveillance studies.(2, 6)

Most of the literature reporting on mortality in eating disorder patients comes from studies examining cohorts in specific treatment settings, which are difficult to compare given the wide variability in treatment target populations, insurance coverage and other selection biases. (8, 9) Several mortality studies report only crude case fatality rates (i.e., they report on deaths among patients with no comparison group or adjustment for expected mortality in the same age population); other studies are limited in sample size or scope and report only on anorexia nervosa and/or only examine female patients.(9, 10) Eating disorders have been misperceived as rare perhaps due to limited awareness of the available data on the burden of disease or a misconception that only the most

severe cases experience a severe burden. (11, 12) Furthermore, the lack of comprehensive data on

eating disorders that includes both males and females has made it difficult to estimate all-cause and

cause-specific mortality among this population.

This study describes all-cause mortality rates within a population-based cohort of patients with

an eating disorder in a context of universal public health care funding. Excess mortality among these

patients wais estimated relative to the general population without an eating disorder using

standardized mortality ratios (SMRs) and potential years of life lost (PYLL) (in total and attributable to

eating disorders). In addition, factors associated with increased hazard of mortality within the ED

cohort were examined including patient socio-demographic and comorbidity measures as well as

indicators of health care service utilization.

METHODS

Study design

This study examines a population-based, retrospective cohort of individuals who received care

for an eating disorder in any hospital in Ontario from January 1, 1990, to December 31, 2013. The

cohort was followed, through record-linkage, until date of death or December 31, 2013, the latest date

possible based on data availability at the time of the analysis).

Data sources

We made use of administrative health care data available through ICES in Toronto, Ontario.

ICES is an independent non-profit organization funded by the Ontario Ministry of Health and holds an

inventory of coded and linkable health datasets, encompassing much of the publicly funded

administrative health services records for the Ontario population eligible for universal health coverage

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since 1986. This data repository includes individual-level, linkable longitudinal data on most publicly

funded health care services. The Registered Persons Database (RPDB), a population-based registry,

contains anonymized demographic data on all insured members of the universal Ontario Health

Insurance Plan (OHIP), such as sex, date of birth, urban or rural dwelling information and

neighbourhood-level income (measured in quintiles at the census tract level). Information on date and

cause of death (where applicable) were obtained from the Ontario Registry General-Death Vital

Statistics. Hospital admissions and associated diagnostic codes used to define the cohort were

obtained from the following health care administrative databases maintained by the Canadian Institute

for Health Information: Discharge Abstract Database (DAD) for non-mental health admissions and

National Ambulatory Care Reporting System (NACRS) for emergency department visits. Psychiatric

hospitalization records were obtained from the Ontario Mental Health Reporting System (OMHRS)

database.

Co-morbidity data for chronic medical conditions were obtained via the following validated

patient cohorts and registries developed, linked and analyzed at ICES including: Ontario Congestive

Heart Failure (CHF) Database; Chronic Obstructive Pulmonary Disease (COPD) Database; Ontario

Diabetes Database (ODD); Ontario Asthma Database; Ontario HIV Database and Ontario Cancer

Registry (OCR). These datasets have been described elsewhere. (13)

Derivation of the eating disorder patient cohort

Individuals were included if they received an eating disorder diagnosis during an emergency

department visit, medical hospitalization, or psychiatric hospitalization from 1990 to 2013. The first

diagnosis from any of these data sources was determined as the cohort entry date. Cohort

development and analyses were carried out with linked administrative health care data holdings at

7

ICES. Diagnostic codes used to identify eating disorder patients included: ICD-9 codes 307.1 (anorexia

nervosa), 307.51 (bulimia nervosa), 307.50 (eating disorders not otherwise specified); ICD-10 codes

F50.0 (eating disorders), F50.1 (anorexia nervosa), F50.2, F50.3 (bulimia nervosa), F50.8, F50.9

(EDNOS), and DSM-IV codes 307.1 (anorexia nervosa), 307.51 (bulimia nervosa), 307.50 (EDNOS). We

restricted our study to these three ED diagnoses because the publicly-funded services in Ontario focus

on the treatment of these ED diagnoses. ED diagnosis codes do not apply to children under the age of

5. Furthermore, children ages 5 to 9 were excluded as the small number of deaths precluded reporting

under Ontario privacy regulations. We excluded individuals who ceased to be publicly insured for

health care at date of cohort entry. This approach resulted in a cohort of 19,041 individuals with and

eating disorder diagnosis (including all patients deceased or alive to the end of December 31, 2013).

The development of this cohort, restricted to individuals alive as of January 1,2014, has also

been described elsewhere. (14)

Analysis

Mortality rates were estimated for the full cohort and were reported as deaths per 1,000

person-years of observation time, overall and by sex (female and male), calendar year (from 1990 to

2013), and age groups. Person-years of follow-up were segregated by sex, calendar year and age

attained over follow-up (to end of follow-up, or death) for each cohort member. This was achieved

using Lexis expansion tools for cohort data using Stata 14 (StataCorp. 2015. *Stata Statistical Software:*

Release 14. College Station, TX: StataCorp LP). Excess mortality in the eating disorder population,

relative to the underlying Ontario population, was illustrated in several ways including SMRs, PYLL in

the cohort, and proportion of PYLL attributable to eating disorder.

SMRs were estimated using the indirect method.(15) SMRs were defined as the number of observed deaths in the eating disorder cohort divided by the number of expected deaths in the cohort if the eating disorder cohort had had the same sex- and age-specific mortality experience as the underlying Ontario population. Expected mortality rates in the general population were obtained using all Ontario deaths in 2011 and corresponding data for the 2011 Census year. SMRs were presented with exact Poisson-based 95% confidence intervals.

Person Years of Life Lost (PYLL) within the eating disorder cohort were estimated as the sum of all years of life lost before age 75 (16) for observed deaths among patients with an eating disorder (expressed as PYLL per 1,000 persons). Expected and excess (eating disorder attributable) PYLL values were also estimated using expected deaths from Ontario 2011 standard mortality rates. The theoretical percent of total PYLL attributable to being in the eating disorder cohort (relative to the underlying population) was defined as attributable PYLL = (total cohort PYLL – expected PYLL)/ total cohort PYLL and expressed as a percentage.

Socio-demographic factors associated with higher risk of mortality within the cohort were examined using Cox Proportional Hazard regression models for all-cause mortality. Patients who entered the cohort with an eating disorder diagnosis on the same day as death contributed no follow-up time and were excluded from the survival models (N=5). Separate Cox models were estimated for patients aged 10 to 44 at entry and those 45 and older. Patient socio-demographic characteristics considered were age, sex and calendar year over the period of the study, as well as neighbourhood-level household income quintile and rurality of residence. Models examining the effect of socio-demographic variables were then further adjusted for medical co-morbidity (i.e., chronic conditions,

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defined beforehand). The adjusted models included six chronic conditions derived from validated

cohorts through administrative databases.

Model diagnostics were performed and indicated no violations of assumptions. This included

confirmation of the validity of a linear effect of age as a continuous covariate in the exponential Cox

model, assessment for non-violation of the assumption of proportional hazards, and lack of excess

multi-collinearity.

Ethics and approvals

ICES is an independent, non-profit research institute whose legal status under Ontario's health

information privacy law allows it to collect and analyze health care and demographic data, without

consent, for health system evaluation and improvement. Thus, the use of data in this project was

authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not

require review by a Research Ethics Board.   The project was approved by the Research Ethics Board at

University Health Network, Toronto.

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RESULTS

Baseline characteristics of the eating disorder cohort are presented in Table 1. Of the 19,041 cohort members, 17,108 were female (89.9%) and 1,933 were male (10.1%). Age at cohort entry ranged from 10 to over 85 years of age, but 88.9% of the population entered the cohort between the ages of 14 and 44. Most of the cohort (88.8%) resided in urban centres. A greater percentage of the cohort lived in middle to low-income neighbourhoods, with 37.4% in the lowest neighbourhood level income category and 18.0% in the middle-income neighbourhood level income category. Categories for eating disorder-specific diagnoses at cohort entry revealed multiple diagnoses for the same individual over time; 31.8% of the cohort had anorexia nervosa alone or in combination with bulimia nervosa and/or eating disorder not otherwise specified (EDNOS); 35.1% of the cohort had a diagnosis of EDNOS alone at enrolment. Eating disorder diagnoses were also comorbid with other medical conditions including asthma (27.0%), diabetes (8.9%), cancer (4.6%) and congestive heart failure (3.5%).

Table 2 presents descriptive statistics for the mortality follow-up analysis of this cohort, including total person-years of follow up and observed deaths, for the whole cohort and by age group and sex. Mortality rates and SMRs by age group and sex are also presented in Table 2. For the entire eating disorder cohort and across all age groups, the all-cause mortality rate was five times higher than expected based on mortality rates in the Ontario population (marginal SMR = 5.06; 95% CI:4.82-5.30). Peak values for SMRs were observed among adults from approximately 30 to 44 years of age. Mortality rates and SMRs were unstable for individuals 10 to 14 due to small number of deaths. SMRs were higher for male eating disorder patients, relative to female, overall and in all age groups. For females, the marginal SMR was 4.59 (95% CI: 4.34-4.85) while for males it was 7.24 (95% CI: 6.58-7.96).

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Excess mortality is further illustrated in Figure 1, which presents cohort and population mortality rates (per 1,000 population) by age and sex as well as age-sex specific SMRs.

The overall expected PYLL (based on expected numbers of deaths in the cohort using the 2011 Ontario age-specific death rates) was estimated at 29.54 years per 1,000 population (95% CI: 28.7-30.4) and similar for each sex separately (Appendix Table 1). Within the eating disorder cohort, estimated total PYLL before age 75 equalled 191.6 per 1,000 population (95% CI: 189.4-193.8), for both sexes, combined. Years of life lost per 1,000 population was higher for males (PYLL within cohort=375.6; 95% CI: 364.7-386.8) relative to females (PYLL within cohort=174.1; 95% CI: 171.9-176.3). For both sexes, the excess PYLL attributable to experiencing an eating disorder was 84%. For female eating disorder patients, it was estimated that 83% of PYLL were attributable to being in the eating disorder cohort; for male eating disorder patients, this value was 92%. Among all Ontario ED patients, over the period of this study, it was estimated that 24,773 years of life were lost due to eating disorder, before the age of 75.

Cox survival models on all-cause mortality, controlling for the effects of demographic characteristics, appear in Table 3. For both age groups (10-44 and >=45 years of age), older age (as a continuous, linear term) and male sex were associated with statistically significant increased mortality risk and adjusted hazard ratio of 1.91 in both age groups. Additionally, mortality declined over calendar years in the analysis showing a statistically significant effect of calendar year on the downward trend in mortality over time (adjusted hazard ratio of 0.9, year over year). In addition, the pattern of association with household income quintile was not a simple linear association, but rather a U-shaped pattern. Higher total mortality hazard ratios were observed in the highest and lowest income quintiles, relative to household income quintiles in the middle.

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Fully adjusted models for age, sex and calendar year resulted in opposite findings for rurality in the analyses for cohort members under and over 45 years of age. Rural residence was associated with lower mortality for cohort members under the age of 45 but higher mortality risk for cohort members 45 or older. Control variables for non-ED chronic medical conditions (CHF, COPD, cancer and HIV) were all positively associated with higher mortality ratios with the exceptions of inverse associations for asthma and diabetes diagnoses within cohort members age 45 and over. For cohort members ages 44 and younger, having a diagnosis of CHF, cancer, diabetes and HIV was positively associated with higher mortality ratios. We observed a simple linear trend toward lower mortality with calendar year of entry into the cohort. This cannot be separated from a general trend in improved survival in the population as age-sex specific mortality risk expected in the population are not updated for each calendar year but based on census years (here based on the 2011 Canadian census).

DISCUSSION

The purpose of this study was to estimate the excess mortality and burden associated with eating disorders using comprehensive population-based data. Notably, this study is among the few internationally that have made use of a population-based eating disorder cohort and to have provided SMR estimates specific to both female and male patients. Our findings show that individuals with eating disorders diagnosed in hospital settings had a mortality rate of approximately 5-fold higher than the general population, with more than 80% of life lost before the age of 75 for females and males.

In female eating disorder patients, we found a roughly five-fold mortality rate relative to the general population. This is similar in magnitude to what has been reported in two international meta-analyses (5, 8) and similar in magnitude to SMRs reported specifically for anorexia nervosa (anorexia

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nervosa being the eating disorder diagnosis with the highest SMRs). Whilst studies have reported on the lifetime prevalence of eating disorders in males ranging from 0.1 to 2.0 for all types,(2, 9) few studies have reported on the mortality rates among males with eating disorders and those studies tend to report exclusively on anorexia nervosa.(17, 18) Our study thus makes a novel and important contribution to the sparse literature on male eating disorder patients and their mortality experience, with a substantially larger sample of male eating disorder patients.

The SMRs observed in males were almost 2-fold higher than in females. This observation of higher mortality in males with eating disorders is particularly concerning as there is evidence to suggest that males are less likely to self-identify or be identified with eating disorders unless the illness severity is~~se~~ are extremely high ~~severe.;~~ ~~A~~additionally~~,~~ ~~,~~ eating disorder treatment centres are less likely to accept ~~or treat~~ male patients (19, 20). ~~Poorer outcomes in male patients with eating disorders may reflect g~~Gender and cultural differences in help--seeking behaviours ~~or referral patterns indicating that~~in male eating disorder patient may result in services ~~for male patients are~~being less accessible, ~~and thus c~~contribut~~ing~~e to worse outcomes. This highlights the need for enhanced case-identification, research and services for male eating disorder patients to improve outcomes (21). We also found that mortality risk was higher amongst younger individuals within the cohort and individuals living in the lowest income neighbourhoods, highlighting issues ~~around potential access~~related to equity of access and quality of care; this warrants further investigation.

While there have been two meta-analyses estimating ED-related mortality, (5, 8) the existing literature has methodological issues including a lack of population-based surveillance data (limited to sub-regional studies and registries from restricted clinical practices(3, 22)), selection of study population, identification of cases, and small sample size.(9, 10, 17, 23-25)

Finally, our results demonstrate the degree to which patients with EDs also experience important medical conditions and co-morbidities, such as congestive heart failure, diabetes, COPD and hypertension amongst others. Mechanisms through which EDs may have a causal impact on diverse chronic diseases have been described elsewhere. (4)

STRENGTHS AND LIMITATIONS

A major strength of our study was the use of a population-based sample, which is more representative and generalizable than cohorts based on a sample of hospitalised patients from individual treatment centres or insurance programs. An additional methodological strength was the use of the recommended SMR method, which is replicable and well established, to report excess mortality relative to the underlying population as well as controlling for sex and age through standardization (as opposed to merely reporting case-fatality rates within the clinical cohort).

One major limitation is the lack of validation of our algorithm for case-detection, which relied on hospital contact data and not outpatient contact data. This may bias towards higher severity of cases and may also truncate the time between illness identification and mortality, which could result in an overestimation of mortality rates.(26) These are limitations of all research involving clinical cohorts based on administrative or insured services data. These inherent limitations of the best data available underscore how important it is to have disease registries for eating disorders established internationally, with high quality clinical measures, which are available only in localized clinical research cohorts (22). Moreover, the lack of data on ethnicity did not allow us to produce ethnic-specific SMRs; future research should seek to address this limitation. Finally, this study included a specific group of ED diagnoses (anorexia nervosa, bulimia nervosa, and ED NOS) for which treatment is

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available in Ontario's publicly funded system. We did not include other eating disorder diagnoses such as binge-eating disorder, and it is unclear whether the findings from our study would generalize to a broader array of eating disorder diagnoses.

IMPACT AND RELEVANCE

In summary, our study provides evidence of the high mortality rate associated with eating disorder diagnoses. Furthermore, males with eating disorders have a higher risk of mortality than females, which underscores the importance of detecting and treating eating disorders in males even though they are relatively low in prevalence. These findings are consistent with previous research on excess mortality; we effectively show the marked gender differences in risk of mortality and actual excess mortality in the eating disorder population. Historically, the burden including mortality, of eating disorders, including mortality, has been documented to a lesser extent compared to studies of other psychiatric conditions despite its prevalence and high mortality rate.

This study serves to highlight the need for ongoing population-based surveillance of eating disorder burden. Early intervention in eating disorders is known to be effective (27) (28) and presents an opportunity to reduce the mortality impact (high and early onset mortality) of these conditions. The inclusion of eating disorders amongst other disorders identified as high priority for improved surveillance and burden of disease data in mental health also highlights a need for better detection of and treatment of eating disorders and associated psychiatric comorbidities to improve long-term outcomes.

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Author Contribution

Data Availability

The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those

who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full

dataset creation plan and underlying analytic code are available upon request, understanding that the

computer programs may rely upon coding templates or macros that are unique to ICES and are

therefore either inaccessible or may require modification.

Declaration of Interest: None

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Tables and Figures

Table 1: Demographic and Clinical Characteristics of the Eating Disorder cohort

VARIABLE	Female	Male	TOTAL	P-VALUE Sex differences (unadjusted)
Age at first diagnosis, *Mean ± SD*	N=17,108 25.76 ± 15.44	N=1,933 37.37 ± 23.91	N=19,041 26.94 ± 16.87	<0.001
	N (% of cohort, females)	N (% of cohort, males)	N (% of cohort)	
Age group at diagnosis				
10_13	1,359 (7.9)	197 (10.2)	1,556 (8.2)	
14_17	5,613 (32.8)	370 (19.1)	5,983 (31.4)	
18_24	4,015 (23.5)	279 (14.4)	4,294 (22.6)	
25_44	4,231 (24.7)	443 (22.9)	4,674 (24.5)	
45_64	1,201 (7.0)	279 (14.4)	1,480 (7.8)	
65_84	519 (3.0)	290 (15.0)	809 (4.2)	
>=85	170 (1.0)	75 (3.9)	245 (1.3)	
Neighbourhood Income Quintile				
1 (low)	3,164 (18.5)	434 (22.5)	3,598 (18.9)	<0.001
2 (medium-low)	3,149 (18.4)	366 (18.9)	3,515 (18.5)	
3 (medium)	3,143 (18.4)	365 (18.9)	3,508 (18.4)	
4 (medium-high)	3,460 (20.2)	377 (19.5)	3,837 (20.2)	
5 (high)	4,105 (24.0)	374 (19.3)	4,479 (23.5)	
Missing	87 (0.5)	17 (0.9)	104 (0.5)	
Rural residence				
No	15,186 (88.8)	1,710 (88.5)	16,896 (88.7)	0.691
Yes	1,922 (11.2)	223 (11.5)	2,145 (11.3)	
Clinical Characteristics				
Eating Disorder Diagnosis at cohort entry				
AN and BN	121 (0.7)	7 (0.4)	128 (0.7)	<0.001
AN and EDNOS	*	*	55 (*)	
AN only	5,437 (31.8)	398 (20.6)	5,835 (30.6)	
AN, BN, and EDNOS	291 (1.7)	7 (0.4)	298 (1.6)	
BN and EDNOS	2,981 (17.4)	353 (18.3)	3,334 (17.5)	
BN only	2,218 (13.0)	137 (7.1)	2,355 (12.4)	
EDNOS only	6,008 (35.1)	1,028 (53.2)	7,036 (37.0)	
Co-morbidity				
Asthma	4,759 (27.8)	480 (24.8)	5,239 (27.5)	0.005
Cancer	638 (3.7)	225 (11.6)	863 (4.5)	<0.001
COPD	1,237 (7.2)	300 (15.5)	1,537 (8.1)	<0.001

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Congestive Heart Failure	472 (2.8)	190 (9.8)	662 (3.5)	<0.001
Diabetes	1,390 (8.1)	343 (17.7)	1,733 (9.1)	<0.001
HIV	23 (0.1)	22 (1.1)	45 (0.2)	<0.001

Legend: SD-standard deviation; AN-Anorexia Nervosa; BN-Bulimia Nervosa; EDNOS-Eating Disorder Not Otherwise Specified; COPD- Chronic Obstructive Pulmonary Disease; HIV, Human Immuno-Deficiency Virus

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Table 2 All-cause mortality comparing the ED cohort to the Ontario population overall and by sex. *

Age group	Person Years (in 1000's)	Observed deaths	Expected deaths	Crude mortality rates (per1,000)	SMR* (per 1000)(95% CI)
Both Sexes					
Overall	155,921.03	1672	330.85	10.88	5.1 (4.8-5.3)
15-19	22,842.62	32	6.72	1.42	4.8 (3.3-6.7)
20-24	29,121.61	59	11.57	2.04	5.1 (4.0-6.6)
25-29	25,621.18	68	10.22	2.66	6.7 (5.3-8.4)
30-34	20,068.30	84	12.04	4.19	7.0 (5.6-8.6)
35-39	14,937.13	92	10.46	6.16	8.8 (7.2-10.8)
40-44	11,810.93	107	12.99	9.06	8.2 (6.8-10.0)
45-49	9,362.66	126	16.85	13.46	7.5 (6.3-8.9)
50-54	6,407.25	116	19.86	18.10	5.8 (4.9-7.0)
55-59	3,871.77	90	18.58	23.25	4.8 (3.9-6.0)
60-64	2,232.77	83	16.3	37.17	5.1 (4.1-6.3)
65-69	1,331.44	105	15.44	78.86	6.8 (5.6-8.2)
70-74	1,012.38	113	18.53	111.62	6.1 (5.1-7.3)
75-79	875.12	137	26.78	156.55	5.1 (4.3-6.1)
80-84	765.24	180	40.25	235.22	4.5 (3.9-5.2)
85-89	474.79	172	42.87	362.26	4.0 (3.5-4.7)
90+	292.76	104	51.06	355.24	2.0 (1.7-2.5)
Female					
Overall	142,655.30	1249	272.29	8.83	4.6 (4.3-4.9)
15-19	20980.86	25	6.21	1.20	4.0 (2.7-6.0)
20-24	27195.17	50	10.83	1.85	4.6 (3.5-6.1)
25-29	24203.29	61	9.66	2.53	6.3 (4.9-8.1)
30-34	18855.12	71	11.31	3.77	6.3 (5.0-7.9)
35-39	13822.51	80	9.68	5.79	8.3 (6.6-10.3)
40-44	10747.7	90	11.82	8.37	7.6 (6.2 -9.4)
45-49	8479.574	106	15.26	12.50	7.0 (5.7-8.4)
50-54	5761.355	94	17.86	16.32	5.3 (4.3-6.4)
55-59	3433.343	73	16.48	21.26	4.4 (3.5-5.6)
60-64	1861.803	61	13.59	32.76	4.5 (3.5-5.8)
65-69	1048.189	70	12.16	66.78	5.8 (4.6-7.3)
70-74	755.4538	67	13.82	88.69	4.9 (3.8-6.2)
75-79	653.2047	85	19.99	130.13	4.3 (3.4-5.3)
80-84	583.2382	114	30.68	195.46	3.7 (3.1-4.5)
85-89	348.6016	119	31.48	341.36	3.8 (3.2-4.5)
90+	236.0726	80	41.17	338.88	1.9 (1.6-2.4)
Male					

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Overall	1,213.18	423	58.56	34.56	7.2 (6.6-8.0)
15-19	1861.75	7	0.5	4.17	13.9 (6.6-29.2)
20-24	1926.44	9	0.74	4.85	12.1 (6.3-23.3)
25-29	1417.89	7	0.56	5.00	12.5 (6.0-26.2)
30-34	1213.182	13	0.73	10.72	17.9 (10.4-30.8)
35-39	1114.625	12	0.78	10.77	15.4 (8.7-27.1)
40-44	1063.231	17	1.17	15.99	14.5 (9.0-23.4)
45-49	883.0904	20	1.59	22.65	12.6 (8.1-19.5)
50-54	645.8871	22	2	34.06	11.0 (7.2-16.7)
55-59	438.4278	17	2.1	38.77	8.1 (5.0-13.0)
60-64	370.974	22	2.71	59.30	8.1 (5.4-12.3)
65-69	283.245	35	3.29	123.57	10.7 (7.7-14.8)
70-74	256.9281	46	4.7	179.04	9.8 (7.3-13.1)
75-79	221.9124	52	6.79	234.33	7.7 (5.8-10.1)
80-84	182.0007	66	9.57	362.64	6.9 (5.4-8.8)
85-89	126.1937	53	11.4	419.99	4.7 (3.6-6.1)
90+	56.68994	24	9.89	423.36	2.4 (1.6-3.6)

*SMRs are stratified by age-group where age is a time-dependent covariate reflecting age attained during follow-up as opposed to at baseline. Time-dependent age calculated using STATA command STSPLIT.

Legend: SMR - standardized mortality ratio; CI – confidence interval

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Table 3 Predictors of relative excess mortality from Cox survival models for all-cause mortality within eating disordered cohort.

	Unadjusted Hazard Ratio	95% Confidence Interval	Adjusted Hazard Ratio	Hazard Ratio 95% Confidence Interval	P-value* (degrees of freedom)
Age 10 to 44- N=16,507					
Age** (integer, continuous)	1.07	(1.06 – 1.07)	1.05	(1.05 – 1.06)	< 0.001 (1)
Calendar year (integer, continuous)	0.90	(0.89 – 0.90)	0.91	(0.91 – 0.92)	< 0.001 (1)
Sex (male versus female)	2.06	(1.92 – 2.21)	1.91	(1.78 – 2.05)	< 0.001 (1)
Neighbourhood income quintile					
1 (low)	1.36	(1.27 – 1.46)	1.26	(1.18 – 1.35)	< 0.001 (4)
2 (medium-low)	0.83	(0.76 – 0.89)	0.81	(0.75 – 0.87)	< 0.001 (4)
3 (medium)	0.95	(0.88 – 1.01)	0.97	(0.89 –1.04)	0.39 (4)
4 (medium-high)	0.96	(0.89 – 1.03)	0.98	(0.91 –1.05)	0.54 (4)
5 (high)			1.00	Reference-	
Rural residence (versus urban residence)	0.65	(0.60 – 0.71)	0.69	(0.63 - 0.75)	< 0.001 (1)
Medical co-morbidity indicators (binary):					
Congestive heart failure			2.45	(2.23 – 2.69)	< 0.001 (1)
COPD			1.07	(0.99 – 1.14)	0.07 (1)
Cancer			2.43	(2.25 – 2.62)	< 0.001 (1)
Asthma			1.01	(0.96 – 1.06)	0.76 (1)
Diabetes			1.75	(1.65 – 1.86)	< 0.001 (1)
HIV			2.16	(1.75 – 2.67)	< 0.001 (1)
Age 45 and older- N=2532					
Age** (integer, continuous)	1.08	(1.08 – 1.08)	1.07	(1.07 – 1.08)	< 0.001 (1)
Calendar year (integer, continuous)	0.88	(0.87 – 0.88)	0.89	(0.88 – 0.89)	< 0.001 (1)
Sex (male versus female)	1.92	(1.82 – 2.01)	1.91	(1.82 – 2.02)	< 0.001 (1)
Neighbourhood income quintile:					
1 (low)	1.47	(1.37 – 1.56)	1.33	(1.25 – 1.42)	< 0.001 (4)
2 (medium-low)	1.11	(1.04 – 1.19)	1.01	(0.94 – 1.08)	0.86 (4)
3 (medium)	1.04	(0.97 – 1.11)	0.93	(0.86 – 0.99)	0.04 (4)
4 (medium-high)	0.85	(0.79 – 0.91)	0.79	(0.74 – 0.85)	< 0.001 (4)
5 (high)			1.00	Reference-	
Rural residence (versus urban residence)	1.27	(1.19 – 1.35)	1.22	(1.15 – 1.30)	< 0.001 (1)
Medical co-morbidity indicators (binary):					
Congestive heart failure			1.32	(1.25 – 1.38)	< 0.001 (1)
COPD			1.06	(1.01 – 1.11)	< 0.03 (1)
Cancer			2.24	(2.14 – 2.35)	< 0.001 (1)
Asthma			0.94	(0.89 – 0.99)	0.03 (1)
Diabetes			0.89	(0.86 – 0.94)	< 0.001 (1)
HIV			2.06	(1.59 – 2.66)	< 0.001 (1)

* Likelihood ratio test for removal of covariate from fully adjusted model shown.
** Age is defined as time-dependent covariate, meaning age of cohort member attained over follow-up and not at baseline. Time-dependent age is calculated using STATA command STSPLIT.
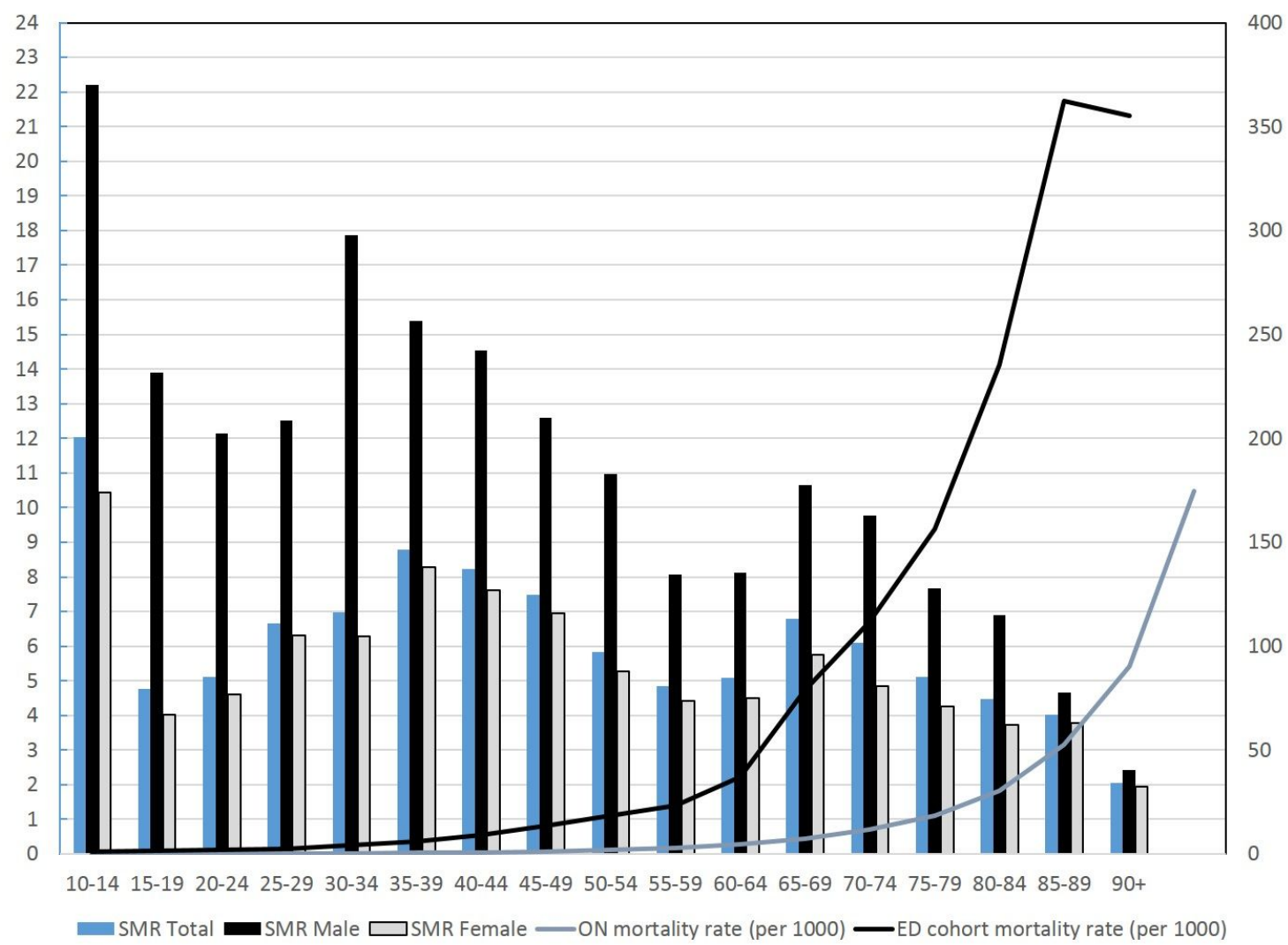**Legend**: COPD- Chronic Obstructive Pulmonary Disease; HIV, Human Immuno-Deficiency Virus

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Appendix Table 1: Age-Sex matched person years of life lost and 95% CI in ED cohort and Ontario population in 2011

	ED Cohort PYLL (95% CI)	Ontario Population PYLL (95% CI)	Excess PYLL (%)
Both Sexes	191.5 (189.3-193.7)	29.6 (28.8-30.5)	85%
Male	375.4 (364.4-386.6)	29.6 (28.7-30.5)	92%
Female	174.8 (172.6-177.0)	29.7 (26.6-32.7)	83%

Legend: ED – eating disorders; CI – confidence interval; PYLL – Person Years of Life Lost

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Figure 1: Standardized mortality ratios-by sex and age-group, all-cause mortality rates observed within the eating disorders cohort (1991-2013) and Ontario (2011) mortality rates

Y1 axis label (left)   Standardized Mortality Ratio (SMR)
Y2 axis label (right)   Observed morality rate (per 1000 person years)

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