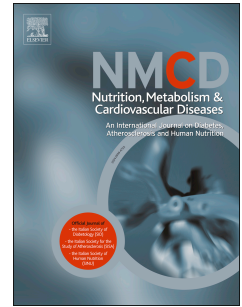# Accepted Manuscript

Mortality from infectious diseases in diabetes

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1   MORTALITY FROM INFECTIOUS DISEASES IN DIABETES

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4   *Running title: infections and diabetes mortality*

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31 **ABSTRACT**

32 **Background and Aims:** to investigate the risk of mortality from infections by comparing the

33 underlying causes of death versus the multiple causes of death in known diabetic subjects living in

34 the Veneto Region, Northern Italy.

35 **Methods and Results:** 185,341 diabetic subjects aged 30-89 years were identified in the year 2010

36 and causes of death were assessed from 2010 to 2015. Standardized Mortality Ratios (SMR) with

37 95% confidence intervals were computed with regional mortality rates as reference. The underlying

38 causes of death and all the diseases reported in the death certificates were scrutinized. At the end of

39 the follow-up, 36,382 subjects had deceased. We observed an increased risk of death from

40 infection-related causes in subjects affected by diabetes with a SMR of 1.83 (95 % CI, 1.71-1.94).

41 The SMR for death from septicemia was 1.91 (95 % CI, 1.76-2.06) and from pneumonia 1.47 (95 %

42 CI, 1.36-1.59). The use of the multiple causes of death approach emphasized the contribution of

43 infectious diseases to mortality.

44 **CONCLUSION:** the results of the present study demonstrate an excess mortality from infection-

45 related diseases in patients affected by diabetes and, more interestingly, show a possible

46 underestimation of the impact of these conditions by routine mortality analyses.

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INTRODUCTION

The prevalence of diabetes is steadily rising, and therefore it constitutes a consistent challenge for health care systems worldwide [1]. In patients affected by diabetes, the main burden in terms of morbidity and mortality is represented by cardiovascular diseases [2], nevertheless infections are increasing both in frequency and severity in these patients [3]. Subjects with diabetes have higher rates of impaired immunity [4,5] and an increased risk for various types of infections when compared with those without diabetes [6] The impact of infectious diseases is particularly high in older patients as recently shown [7,8]. The association of diabetes and infections has been reported in the past and at least two important studies have observed an increased frequency of bacteriuria and bacteremia in adult women with diabetes versus those without it [9,10]. Besides bacteremia, diabetes has shown to increase the risk of pneumonia, tuberculosis, urinary tract infections, severe gram-positive and hospital acquired post-operative infections [3,11].

It has been reported that 28-day mortality rate is higher among patients affected by diabetes with MRSA pneumonia compared to patients without diabetes [12]. Nevertheless, other studies did not report an increased risk of mortality from community acquired pneumonia in patients with diabetes [13]. An important Australian study, that involved 1,108,982 individuals with diabetes, reported an increased risk of mortality from various infections compared to the general population [14]. The risk of mortality was higher in type 1 patients compared to type 2 patients [14].

The excess risk of death from infectious diseases in patients with diabetes may be multifactorial. An important role is played by the presence of microangiopathy and renal failure [15]. The other important factor is hyperglycemia: hyperglycemia on admission has been shown to increase the risk of pneumonia-related mortality [16].

Considering the important emerging role of infectious diseases in the clinical outcomes of diabetes, in the present study we analyzed the impact of infections on the risk of mortality in patients with

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77 diabetes by using both the underlying cause of death (UCOD) and the multiple causes of death

78 (MCOD) approaches [17]. Through the MCOD approach, it is likely to obtain a more realistic

79 estimate of mortality burden from infection-related causes [17].

80 **METHODS**

81 **Identification and follow-up of a cohort of diabetic subjects**

82 In the Veneto Region (North-Eastern Italy), hospital care is free of charge, while patients contribute

83 to out-of-hospital care and drug costs. However, after the certification by a specialist and the

84 enrollment in an electronic list of subjects with diabetes maintained by Local Health Units, out-of-

85 hospital care related to diabetes (both type 1 and type 2) is free of charge. The electronic regional

86 archive of subjects with copayment exemption for diabetes is estimated to include about 80% of

87 subjects identified as diabetics by multiple data sources [18]; therefore it does not include all the

88 affected residents in the Region because, for example, elderly patients with an income below an

89 official threshold have access to free outpatient care even if not listed as diabetic subjects. However,

90 such archive can be the source for the identification of a large cohort of patients; in a previous

91 survey in the Veneto Region, the positive predictive value of the archive was 98% for the diagnosis

92 of diabetes in a sample of people aged 18–65 years [19].

93 For the purpose of this study, we identified in the electronic archive of the Veneto Region a cohort

94 of diabetic patients aged 30-89 years with copayment exemption for diabetes in January 2010 and

95 linked them with the archive of causes of deaths occurred in the period 2010-2015. Based on

96 copayment exemptions, selected comorbidities affecting patients with diabetes were also identified:

97 cancer, chronic renal failure, heart diseases (congestive heart failure, ischemic and hypertensive

98 heart diseases), respiratory diseases (chronic respiratory failure, asthma), rheumatoid arthritis,

99 Parkinson's disease, and having received an organ transplant. The study was carried out by using

100 health records previously submitted to a standardized anonymization process assigning to each

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101 subject a unique code allowing record linkage between electronic archives, without any possibility

102 of retrieving the identities of patients. Each subject was followed-up from January 1, 2010, either

103 until death, or 90 years of age, or December 31, 2015, whichever came first.

Analysis of causes of death

105 A copy of death certificates of all residents in the Veneto Region is centrally transmitted to the

106 Regional Epidemiological Department for coding of causes of death according to the International

107 Classification of Diseases, 10th Edition (ICD-10). Since 2008 the electronic regional archive of

108 mortality includes not only the underlying cause of death, but all diseases mentioned in the death

109 certificate (MCOD), both in Part I (i.e. conditions involved in the causal chain of events leading to

110 death), and in Part II (i.e. other significant conditions contributing to death). The selection of the

111 UCOD is performed by means of the Automated Classification of Medical Entities, which is a

112 computer program developed by the US National Center for Health Statistics to standardize

113 assignment of the underlying cause [20].

114 To assess mortality in the study cohort, common causes of death routinely reported in mortality

115 statistics were investigated, including certain infectious diseases (ICD-10 A00-B99), sepsis (A40-

116 A41), and pneumonia (J12-J18). Furthermore, to obtain a broader picture of infections-related

117 deaths, the following causes were included in a single category: certain infectious diseases (A00-

118 B99, with the exclusion of viral hepatitis B15-B19), respiratory infections (J10-J22, J69, J85-J86),

119 and urinary infections (N10-N12, N136, N15, N390). Mention of infection diseases was searched

120 both limited to the UCOD, and among MCOD of the period 2010–2015.

121 Since all analyses were carried out on routinely collected anonymized health records, the study was

122 deemed exempt from approval by the Local Ethical Committee.

Statistical analysis

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124 Standardized Mortality Ratios (SMR) with 95% confidence intervals based on the Poisson

125 distribution were computed as the ratios between deaths observed in the diabetic cohort, and those

126 expected according to age- and gender-specific regional mortality rates. SMRs were computed for

127 both total mortality and the main nosologic categories based on the underlying cause of death.

128 SMRs were assessed in the whole cohort of diabetic subjects, separately by gender and three classes

129 of age, and stratified by the presence of comorbidities.

130 Furthermore, the proportional mortality (share of overall mortality accounted by a specific cause)

131 for infectious diseases was analyzed by follow-up period (2010-2012 and 2013-2015), both through

132 the UCOD and the MCOD approaches.

133 **RESULTS**

134 In the present study, 185,341 patients with diabetes were included out of 191,301 identified on

135 January 2010: 5,960 were excluded for the age limits (< 30 yrs or ≥ 90 yrs). Less than 1 % of

136 patients were lost during the years of follow-up. At the end of the follow-up 36,382 (24.7 %)

137 patients had deceased. The main cause of death, in quantitative terms, was represented by

138 cardiovascular diseases (as shown in table 1), nevertheless the risk of dying from infection-related

139 causes was quite high, with a SMR of 1.83 (95 % CI, 1.71-1.94). The SMR for death from

140 septicemia was 1.91 (95 % CI, 1.76-2.06) and that from pneumonia 1.47 (95 % CI, 1.36-1.59),

141 respectively. It is worth noting that the highest SMRs, with a two-fold increased risk of mortality

142 with respect to the general population, were observed for sepsis as well as for few already well-

143 known causes of death in diabetic subjects: ischemic heart diseases, liver and pancreatic cancer, and

144 chronic liver diseases.

145 Table 2 reports the number of deaths and SMRs for infection-related deaths stratified by sex and

146 age. In general, SMRs decreased with increasing age in all conditions and the peaks of SMRs were

147 seen in the group aged 30-64 yrs in both sexes. Females showed higher SMRs, especially in the

148 younger age group. The highest risk of dying from infection-related causes was for sepsis, with a 3

149 and about 5 fold increase in males and females, respectively, aged 30-64 yrs (table 2). The SMRs

150 for pneumonia in the same age group was 2.18 (95 % CI, 1.16- 3.73) for males and 3.53 (95 % CI,

151 1.25- 7.68) for females. Of note, figure 2 shows the prevalence of infectious diseases when selected

152 as the UCOD, or as any mention in the death certificate (MCOD). This figure emphasizes that

153 infections may largely be underestimated as causes of death. A large difference between UCOD and

154 MCOD could be observed especially during the second triennium of follow-up for which sepsis was

155 the main contributor (figure 2). From 2013 to 2015, infectious diseases were selected as the UCOD

156 in 6.0% of overall deaths, whereas they were mentioned in 20.6% of all death certificates in diabetic

157 subjects. Table 3 shows the SMRs for common infections and sepsis stratified according to the

158 comorbidities. The increased risk of death from infections persisted after stratification for the

159 comorbidities. Some subgroups in the sepsis analysis have few events, but it is still shown that the

160 trend of SMRs indicates an increase in the risk of mortality.

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DISCUSSION

163 The main results of this study were: 1) patients with diabetes experienced an excess mortality from

164 infectious diseases that persisted even when the comorbidities were accounted for by stratified

165 analysis, 2) excess mortality peaked in younger patients (between 30-64 yrs) and declined

166 afterwards, 3) SMRs of mortality were higher in females, and 4) the burden of infectious diseases

167 on mortality became substantial when the MCOD approach was adopted; therefore the use of

168 UCOD may lead to an underestimation of infectious diseases as cause of death. In the second

169 triennium of follow-up there was an increase in infection-related mortality and sepsis was the major

170 contributor to this increase.

171 Notably, about 20% of patients with diabetes could not be included in the study, mainly elderly

172 patients with low economic income. This may represent a selection bias that limits the

173 generalization of our results. However, this bias may also lead to a further underestimation of the

174 impact of infectious diseases on total mortality.

175 During the recent years, infectious diseases have turned out to be a major health problem probably

176 due to the emergence of multi-resistant bacteria [11,12,13], and the growing number of patients

177 with altered immune function. Diabetes may compromise the immune system activity at several

178 levels [3,21].

179 A retrospective study on 218,805 elderly patients with diabetes showed an high incidence of

180 community acquired infection (lower respiratory tract and urinary tract infections, sepsis) with

181 many of them requiring hospitalization [7]. In England, between 2000-2001 and 2010-2011,

182 hospital admission rates for community-acquired infection more than doubled [8]. Our results

183 showed an increase in infectious diseases in the interval 2013-2015 compared to 2010-2012. The

184 increase for sepsis was impressive, maybe related both to a real increase and to more careful

185 recording of the condition in death certificates [17].

186 In the younger age group (30-64 yrs), the risk of dying from sepsis or pneumonia was 3-5 and 2-3.5

187 fold higher in patients with diabetes, with higher relative risks observed in the female gender.

188 Eventually, the risk of dying from infection-related causes decreased with age. Diabetes is

189 associated with an increased risk of mortality from different infectious diseases [14] and infections

190 caused by specific agents such as Pseudomonas aeruginosa [22] or Acinetobacter baumannii [23] .

191 Our results are in agreement with a recent and large population-based study from Australia [14].

192 This Australian study found comparable SMRs for sepsis , while SMRs for pneumonia were higher

193 in the present study. The Australian study is also important because the authors were able to

194 distinguish between type 1 and type 2 diabetes, observing higher risks in type 1 diabetes.

195 However, instead of recoding the causes of death and conducting a successive analysis as in the

196 Australian study [14], we analyzed any mention of infections in death certificates. We believe that

197 this latter approach can better estimate the global burden of infectious diseases on mortality,

198 contributing also to emphasize the underestimation of the real impact of these diseases on mortality

199 as shown by our results (figure 2) [17].

200 Community-acquired pneumonia, despite modern treatment modalities, still confers a high in-

201 hospital and 30-day risk of mortality [24]. Diabetes is one among all the comorbidities that can

202 increase the risk of mortality in these patients [24]. Moreover, the 28-day mortality in patients with

203 diabetes affected by nosocomial pneumonia caused by methicillin-resistant microorganisms was

204 higher compared to patients without diabetes [12]. The risk of death was sixth-fold higher among

205 patients with diabetes who were receiving chronic renal dialysis [12].

206 The relationship among diabetes, immune system function and infections may be mediated by

207 multiple factors, but at least three of them deserve attention: microangiopathy, renal dysfunction

208 and other comorbidities, as well as short and long-term hyperglycemia.

209 Microangiopathy along with hyperglycemia may alter both the permeability and the structure of

210 glycolipid moiety in the microcirculation [25] increasing the risk of bacteremia [3].

211 Renal dysfunction seems to be a critical factor of infection-related mortality, as reduced glomerular

212 filtration rate has been associated to an increased risk (more than double when GFR falls below 30

213 ml/min/1.73m^2) of mortality from infection-related conditions [26] . Even the pre-existence of

214 chronic kidney disease is associated with an increased short-term risk of mortality following

215 pneumonia and sepsis [27].

216 Comorbidities may play an important role in causing the excess mortality from infectious diseases;

217 a retrospective cohort study found an increased risk for infection-related mortality in adults with

218 diabetes and reported that the increased risk could be mediated by congestive heart failure [28].

219 However, our study seems to indicate that the risk of mortality from infections was increased even

220 after stratification by comorbidities (table 3).

221 Hyperglycemia was shown to impair the chemotaxis of neutrophils, phagocytosis, superoxide

222 production and killing activity of Staphylococcus aureus [29]. Also short-term episodes of

223 hyperglycemia may impair IL-6 expression in intermediate monocytes and IL-17A expression, both

224 of which are responsible for immune dysfunction in critically ill patients [30]. However, the

225 relationship between glycemia and sepsis is not straightforward. In recent studies it has been shown

226 that while diabetes mellitus behaves somehow as a protective factor in sepsis patients, hyper- or

227 hypoglycemia status on admission, and increased blood glucose variability during hospital stay,

228 were independently associated with an increased risk of mortality [31].

229 Through all the above mechanisms, patients affected by diabetes are at increased risk of mortality

230 from infection-related diseases. Our results may have important clinical relevance as they show that

231 the impact on mortality from infectious diseases, including sepsis, may be largely underestimated if

232 confined to the UCOD. In fact, the UCOD usually emphasizes the impact of chronic illnesses and

233 understates the role of infections in the terminal phase leading to death, while MCOD, by analyzing

234 all conditions reported in the death certificate, may reveal a more realistic picture of the impact of

235 infections as a cause of mortality [17].

236 Our study may have important clinical implications as it suggests that infectious diseases greatly

237 increase the risk of a worse prognosis in patients affected by diabetes. Even though the absolute risk

238 based on the UCOD is quite small, it should be emphasized that the real impact of infectious

239 diseases on mortality may be largely underestimated, as the use of MCOD seems to indicate.

240 The present study has different strengths: standardized coding of death certificates, inclusion of

241 deaths in non-hospitalized patients, the large number of subjects, and the use of both UCOD and

242 MCOD for classifying infection-related causes of death. Limitations of the study are the use of a

243 single source of identification of diabetes, the lack of distinction between type 1 and type 2 diabetes

244 and, finally, the absence of clinical variables such as severity of diabetes, diabetes duration,

245 glycated hemoglobin and type of hypoglycemic treatment that are difficult to obtain by

246 administrative databases.

247 In conclusion, the results of the present study demonstrate an excess mortality from infection-

248 related diseases in patients affected by diabetes and, more interestingly, show a possible

249 underestimation of the impact of these conditions in causing mortality.

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Table 1. Number of deaths and standardized mortality ratio (SMR) with 95% Confidence Interval (CI) in a cohort of 185,341 patients with diabetes according to the underlying cause of death. Reference = expected deaths based on gender- and age-specific mortality rates in the Veneto Region (Italy), 2010-2015.

	n deaths	SMR (CI)	% all deaths
Certain infectious and parasitic diseases (A00-B99)	1,022	1.83 (1.71-1.94)	2.8%
Septicemia (A40–A41)	641	1.91 (1.76-2.06)	1.8%
Neoplasms (C00-D48)	10,870	1.31 (1.28-1.33)	29.9%
Malignant neoplasms of colon, rectum and anus (C18-C21)	1,048	1.24 (1.17-1.32)	2.9%
Malignant neoplasm of liver (C22)	1,194	2.26 (2.14-2.40)	3.3%
Malignant neoplasm of pancreas (C25)	1,159	1.85 (1.74-1.96)	3.2%
Malignant neoplasms of trachea, bronchus and lung (C33-C34)	2,058	1.17 (1.12-1.22)	5.7%
Malignant neoplasm of breast (C50)	526	1.26 (1.15-1.37)	1.4%
Endocrine, nutritional and metabolic diseases (E00-E90)	4,814	5.17 (5.03-5.32)	13.2%
Diabetes mellitus (E10-E14)	4,518	6.08 (5.90-6.26)	12.4%
Mental and behavioural disorders (F00-F99)	822	0.98 (0.92-1.05)	2.3%
Dementia (F00-F03)	785	1.02 (0.95-1.09)	2.2%
Diseases of the nervous system (G00-G99)	914	0.90 (0.84-0.96)	2.5%
Diseases of the circulatory system (I00-I99)	12,282	1.53 (1.50-1.55)	33.8%
Hypertensive diseases (I10-I15)	1,261	1.26 (1.19-1.33)	3.5%
Ischemic heart diseases (I20-I25)	5,085	1.80 (1.75-1.85)	14.0%
Other heart diseases (I00-I09, I26-I51)	2,855	1.49 (1.43-1.54)	7.8%
Cerebrovascular diseases (I60-I69)	2,707	1.41 (1.35-1.46)	7.4%
Diseases of the respiratory system (J00-J99)	2,088	1.26 (1.21-1.31)	5.7%
Pneumonia (J12-J18)	665	1.47 (1.36-1.59)	1.8%
Chronic lower respiratory diseases (J40–J47)	752	1.13 (1.05-1.21)	2.1%
Diseases of the digestive system (K00-K93)	1,618	1.72 (1.64-1.80)	4.4%
Diseases of liver (K70-K76)	799	2.31 (2.15-2.48)	2.2%
Diseases of the genitourinary system (N00-N95)	550	1.66 (1.52-1.80)	1.5%
External causes of mortality (V01-Y84)	910	1.30 (1.22-1.39)	2.5%
All causes	36,382	1.53 (1.51-1.54)	100.0%

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358 **Table 2**. Number of deaths and standardized mortality ratio (SMR) with 95% Confidence Interval
359 (CI) in patients with diabetes, by gender and age class according to the underlying cause of death.
360 Reference = expected deaths based on gender- and age-specific mortality rates in the Veneto Region
361 (Italy), 2010-2015.

	Males			Females		
	n	SMR (CI)	% all deaths	n	SMR (CI)	% all deaths
All causes						
30-64 yrs	2,209	2.18 (2.09-2.27)	-	729	2.47 (2.29-2.65)	-
65-74 yrs	5,644	1.72 (1.67-1.76)	-	2,349	1.95 (1.88-2.04)	-
75-89 yrs	13,159	1.35 (1.33-1.38)	-	12,292	1.48 (1.46-1.51)	-
Sepsis						
30-64 yrs	30	3.00 (2.02-4.28)	1.4%	16	4.98 (2.84-8.08)	2.2%
65-74 yrs	90	2.44 (1.96-3.00)	1.6%	52	3.67 (2.74-4.81)	2.2%
75-89 yrs	233	1.63 (1.43-1.85)	1.8%	220	1.72 (1.50-1.96)	1.8%
Pneumonia						
30-64 yrs	13	2.18 (1.16-3.73)	0.6%	6	3.53 (1.29-7.68)	0.8%
65-74 yrs	57	1.91 (1.45-2.47)	1.0%	33	3.21 (2.21-4.51)	1.4%
75-89 yrs	306	1.38 (1.23-1.55)	2.3%	250	1.37 (1.20-1.55)	2.0%
Common infections*						
30-64 yrs	70	1.96 (1.53-2.48)	3.2%	38	4.02 (2.84-5.51)	5.2%
65-74 yrs	205	1.79 (1.55-2.05)	3.6%	113	2.42 (1.99-2.91)	4.8%
75-89 yrs	753	1.33 (1.23-1.43)	5.7%	692	1.30 (1.20-1.40)	5.6%

362 *Common infections: some infectious diseases A00-B99 - with the exclusion viral hepatitis B15-
363 B19; respiratory infections J10-J22, J69, J85-J86; urinary infections N10-N12, N136, N15, N390

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Table **3**. Number of deaths and standardized mortality ratio (SMR) with 95% Confidence Interval (CI) in patients with diabetes, by gender and comorbidities according to the underlying cause of death. Reference = expected deaths based on gender- and age-specific mortality rates in the Veneto Region (Italy), 2010-2015.

	Males		Females	
	N	SMR (CI)	n	SMR (CI)
Common infections*				
No comorbidities	540	1.25 (1.14-1.36)	478	1.22 (1.11-1.33)
Any comorbidity	488	1.71 (1.57-1.87)	365	1.85 (1.67-2.05)
Cancer	123	1.35 (1.12-1.61)	85	1.50 (1.19-1.85)
Chronic renal failure	47	4.09 (3.00-5.44)	28	5.17 (3.44-7.48)
Heart diseases	344	1.71 (1.53-1.90)	260	1.88 (1.66-2.12)
Respiratory diseases	29	1.96 (1.31-2.81)	21	2.25 (1.39-3.44)
Rheumatoid arthritis	14	4.39 (2.40-7.36)	15	2.36 (1.32-3.90)
Parkinson's disease	13	2.98 (1.58-5.09)	9	2.24 (1.02-4.26)
Transplant	8	9.27 (3.99-18.3)	5	22.8 (7.35-53.2)
Sepsis				
No comorbidities	188	1.63 (1.41-1.88)	165	1.69 (1.45-1.97)
Any comorbidity	165	2.21 (1.88-2.57)	123	2.55 (1.12-3.04)
Cancer	42	1.76 (1.27-2.37)	23	1.62 (1.03-2.43)
Chronic renal failure	18	5.87 (3.48-9.28)	15	11.3 (6.30-18.6)
Heart diseases	119	2.25 (1.87-2.70)	90	2.69 (2.16-3.31)
Respiratory diseases	4	1.04 (0.28-2.66)	6	2.55 (0.93-5.55)
Rheumatoid arthritis	5	5.87 (1.89-13.7)	3	*1.88 (0.38-5.48)*
Parkinson's disease	3	*2.64 (0.53-7.72)*	5	5.23 (1.68-12.2)
Transplant	3	*11.5 (2.30-33.5)*	2	*30.0 (3.37-108)*

*Common infections: some infectious diseases A00-B99 - with the exclusion viral hepatitis B15-B19; respiratory infections J10-J22, J69, J85-J86; urinary infections N10-N12, N136, N15, N390

383 **FIGURE LEGENDS**

384 Figure 1. Contribution of infectious diseases selected as the underlying cause of death (UCOD), or
385 contributing causes of death, among 36,382 decedents from a cohort of 185,341 patients with
386 diabetes. The results are stratified by the two triennial periods of the follow-up.
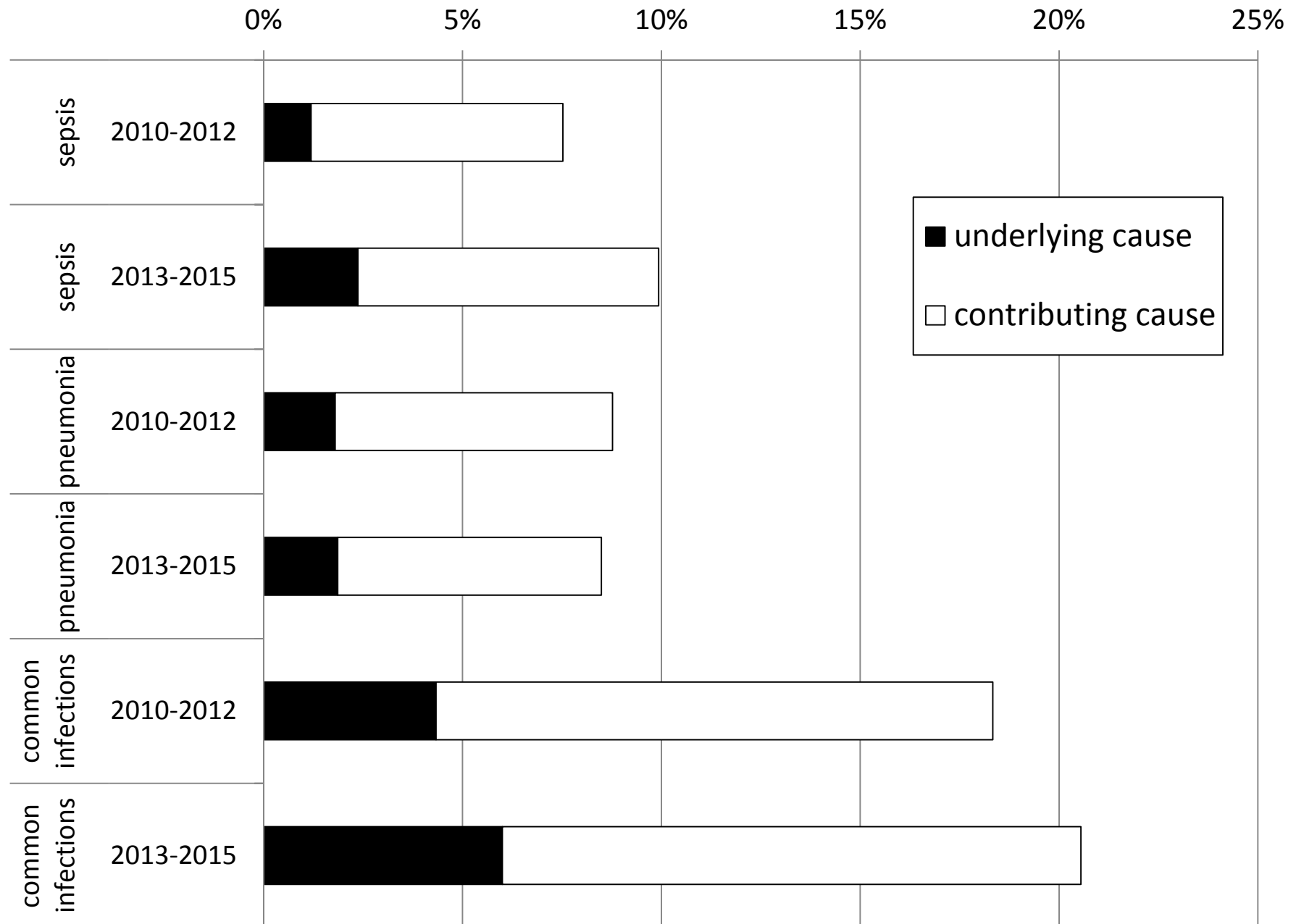
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Highlights

Infections are growing as a major problem in diabetes.

The risk of dying from infections in diabetes is quite high.

Septicemia and pneumonia are major threatens.

Multiple causes of death approach may give a more realistic estimate of mortality.