Excess mortality in mothers of patients with polycystic ovary syndrome

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STUDY QUESTION: Do diabetic parents of patients with polycystic ovary syndrome (PCOS) encounter excess mortality compared with the mortality of men and women with type 2 diabetes, recruited without selection for PCOS?

SUMMARY ANSWER: Type 2 diabetes among mothers of PCOS patients results in excess mortality compared with women with diabetes from the general population.

WHAT IS KNOWN ALREADY: Insulin resistance is a prominent feature of PCOS. Because of the heritable nature of PCOS, parents of these patients are also prone to develop type 2 diabetes mellitus, which might influence their life expectancy.

STUDY DESIGN, SIZE, DURATION: This reverse parent-offspring study included 946 mothers and 902 fathers of patients with PCOS.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The medical history of the parents was primarily obtained during the initial screening of each patient and updated via questionnaires. Mortality data of these parents were compared with the mortality rates of the general Dutch population and with mortality rates of a control population consisting of 1353 men and women diagnosed with type 2 diabetes mellitus. The standardized mortality ratio (SMR) was calculated as the ratio of the observed mortality of the parents to the expected mortality in the general Dutch population. The mortality of parents with type 2 diabetes mellitus relative to controls with diabetes but not related to anyone with PCOS was standardized for age, gender and calendar period using Poisson regression.

MAIN RESULTS AND ROLE OF CHANCE: In total, 302 parents were deceased in 62 693 person-years. Mothers above age 60 had a significant excess mortality of 1.50 (95% CI 1.15–1.92) compared with the general Dutch population. Moreover, mothers with diabetes had two-times higher mortality risk compared with control women with diabetes (RR 2.0, 95% CI 1.19–3.41). No excess mortality among fathers of PCOS patients was observed.

LIMITATIONS, REASON FOR CAUTION: Although recall bias for family history was previously demonstrated to be minimal for long-term chronic diseases, the prevalence of diabetes in the parents was based on their daughter’s self-report and was not clinically confirmed. Also, no other additional clinical data regarding the parent population were available. Prospective long-term follow-up studies should be conducted to confirm this excess mortality.

WIDER IMPLICATIONS OF THE FINDINGS: Our findings justify screening for type 2 diabetes mellitus among the mothers with a daughter suffering from PCOS to ensure that timely preventive and therapeutic measures according to the appropriate guidelines can be taken.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age with a prevalence of 6–10% in an unselected population (Azziz et al., 2004). PCOS is a life-long condition with considerable variation of symptomatology between and within patients over time (ESHRE ASRM Sponsored PCOS Consensus Workshop Group, 2012). The syndrome is characterized by ovulatory dysfunction, hyperandrogenism and polycystic appearance of the ovaries (ESHRE ASRM Sponsored PCOS Consensus Workshop Group, 2004). Insulin resistance is also a prominent feature of PCOS (Dunaif, 1989), and a higher rate of impaired glucose tolerance, gestational diabetes and type 2 diabetes mellitus has been found in patients with PCOS compared with controls (Legro et al., 1999; Boomsma et al., 2008). Obesity is present in up to 60% of all patients with PCOS and is an exacerbating factor for the development of insulin resistance, impaired glucose tolerance and type 2 diabetes mellitus (Barber et al., 2007). Type 2 diabetes mellitus increases the risk of cardiovascular disease and reduces life expectancy (Haffner et al., 1998). Studies assessing mortality rates of patients with PCOS and their family members are currently scarce due to small sample sizes and limited follow-up times of the patients (Pierpoint et al., 1998; Davies et al., 2011; Schmidt et al., 2011; Morgan et al., 2012).

Genetic factors play an important role in the etiology of PCOS, as suggested by the estimated heritability of 65% (Vink et al., 2006). The syndrome itself and notably the associated co-morbidities both cluster in families. Parents of patients with PCOS more often have insulin resistance compared with age- and BMI-matched controls with a healthy daughter (Sir-Petermann et al., 2002; Yilmaz et al., 2005). Consequently, they seem to be at increased familial risk of developing cardiometabolic problems (Sam et al., 2006). A previous study indicated that fathers of patients with PCOS had a higher prevalence of heart attacks and strokes compared with a reference population (Taylor et al., 2011). Moreover, an increase has been observed in premature cardiovascular events among mothers of patients with PCOS (Cheang et al., 2008). Whether the presence of diabetes plays a role in this increased cardiovascular risk is insufficiently known.

We hypothesized that the susceptibility to type 2 diabetes mellitus explains an important part of the complications among the patients with PCOS and their parents. Long-term follow-up studies, with adequate sample sizes and well-phenoyped patients with PCOS, assessing mortality, the most indisputable outcome, are ongoing but still require approximately three decades of follow-up. Because of the high heritability of PCOS and to overcome the lack of appropriate follow-up data, we determined all-cause mortality in parents of patients with PCOS compared with the mortality in the general Dutch population. Moreover, we determined all-cause mortality of parents with type 2 diabetes mellitus compared with the mortality of men and women with type 2 diabetes, but recruited without selection for PCOS. The overall aim of our study was to determine whether PCOS is related to excess mortality in an offspring-parent analysis.

Methods

PCOS diagnosis and assessment

Women with oligomenorrhea (interval of menstrual periods of at least 35 days) or amenorrhea (absence of vaginal bleeding for over 6 months) were examined at the outpatient clinic for cycle disturbances at the Erasmus MC University Medical Center Rotterdam. Prior to their appointment, patients fill out a questionnaire which is discussed with the physician during their visit. Patients underwent a standardized initial examination that was performed after an overnight fast. Clinical examination included age, ancestry, menstrual history as well as current cycle length and cyclicity, height and weight, body mass index (BMI), Ferriman–Gallwey (FG)-score and waist circumference. Transvaginal ultrasonography was performed to assess mean ovarian volume and mean follicle count for both ovaries. This clinical work up has been described previously (Imani et al., 1998). Diagnosis of PCOS was based on the Rotterdam criteria (ESHRE ASRM Sponsored PCOS Consensus Workshop Group, 2004). Informed consent from every patient who visited the outpatient clinic was obtained, according to international review board standards of the Erasmus MC University Medical Center Rotterdam. This protocol has been approved by the medical ethical review board of the Erasmus MC University Medical Center Rotterdam according to the Declaration of Helsinki.

Endocrine assessment

All patients underwent a standardized initial examination that was performed after an overnight fast in the morning between 08:00 and 11:00 am. Blood samples were obtained by vena puncture and processed within 2 h. Serum was stored at −20°C until assayed. Endocrine evaluation included determination of serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), sex hormone binding globulin (SHBG) and androstenedione (AD). Immunoradiometric assays were used to measure LH, FSH, T, SHBG, AD and insulin. Glucose levels were measured using a Hitachi 917 analyzer (Roche Diagnostics, Almere, The Netherlands).

Intra-assay and inter-assay coefficients of variation were <5% for FSH, <5% for LH, <8% for SHBG, <8% for T, <4% for AD, <5% for insulin, <8% for insulin, <10% for T and <11% for FSH, and <6% and <8% for insulin, respectively. The free androgen index (FAI = 100(T (nmol/liter)/SHBG (nmol/liter))) was calculated.

Parental life years and parental medical history

Birth dates and mortality dates of the parents were obtained from a nationwide web-based municipal record database (Dutch name: Gemeentelijke Basisadministratie Persoonsgegevens, GBA). This nationwide municipal database contains official records of births, marriages, and deaths of all government registered people living in the Netherlands and the Netherlands Antilles. Parental person-years were calculated by using dates of birth, death and censoring (end of follow-up: 1 January 2007). In case this information was untraceable for both parents, the patient was excluded from further analyses. The parental medical history was primarily obtained during the initial screening of the patient. To complete and update the information about the prevalence of type 2 diabetes and cardiovascular disease in their parents, a questionnaire was sent to all screened patients with PCOS.
Population-based cohort of patients diagnosed with type 2 diabetes mellitus

Mortality rates of men and women diagnosed with type 2 diabetes mellitus were collected from the Zwolle Outpatient Diabetes Project Integrating Available Care (ZODIAC) study. This large diabetes project was initiated in 1998 in the Zwolle region of the Netherlands. In its first phase, general practitioners were assisted by hospital-based diabetes specialist nurses in providing care for patients with type 2 diabetes. Patients with a very short life expectancy and patients with insufficient cognitive abilities were excluded. A total of 1353 (90%) patients agreed to participate in the study. The details of this study have been published previously (Ubink-Veltmaat et al., 2005). The ZODIAC study was approved by the local medical ethics committee and all included subjects provided informed consent.

Statistical analysis

Baseline characteristics of the patients with PCOS were evaluated using a commercially available statistical package (IBM Statistical Package of the Social Science/Predictive Analytic Software version 20). Because of non-normality, data were expressed as median and interquartile ranges for continuous variables. Categorical variables were expressed as number and percentage. Mann–Whitney U tests and Chi-square tests, if necessary with continuity correction, were performed to compare baseline characteristics of the patients.

The all-cause mortality of the parents of the patients with PCOS was compared with the all-cause mortality of men and women from the general Dutch population standardized for age, gender and calendar period, as previously described (VandenBroucke, 1982; Coleman et al., 1989). The ratio of the observed to the expected numbers of deaths is the standardized mortality ratio (SMR). The expected mortality was calculated by multiplying the total number of years lived by the study population until 1 January 2007 in each calendar period, with the age- and gender-specific mortality rates in the Dutch general population for each calendar period. These data are available at Statistics Netherlands using software of the World Health Organization (Coleman et al., 1989).

Statistics Netherlands is responsible for collecting and processing data of a multitude of societal aspects including mortality rates. The parental years before birth of the patient with PCOS were excluded from the analyses. Including these years would lead to selecting years without deaths, resulting in underestimation of the mortality risk. Calendar periods were divided into 5-year intervals, and to each of these intervals we applied the population mortality rates. We also calculated the SMR in different age groups. The 95% confidence interval (CI) of the SMR was calculated assuming a Poisson distribution of the observed number of deaths and by using exact limits (VandenBroucke, 1982). The SMRs of the diabetic patients, who were recruited from the general population by calculating the relative risk (RR) standardized for age, gender and calendar period. A P-value of <0.05 was considered to be statistically significant.

Results

In total 1088 patients diagnosed with PCOS were eligible. Of these, the address of 130 patients could not be traced. They were therefore considered as lost to follow-up. Dates of birth, death and censoring of at least one parent were available for the remaining 958 (88.1%) patients with PCOS. Baseline characteristics of included and excluded patients with PCOS are shown in Table I. PCOS features and associated characteristics were very similar in both groups.

First, we evaluated whether having a daughter with PCOS influenced all-cause mortality. Information on birth and mortality dates was available for 1848 (96.5%) of the 1916 parents, i.e. 946 (98.7%) of the mothers and 902 (94.1%) of the fathers. A total of 302 deaths were observed in 62694 person-years (Table II). In total, 586 patients with PCOS replied to the questionnaires, resulting in a response rate of 61.2% (586 out of 958). In total, 56.3% of the patients for whom information on medical health was available, did not had type 2 diabetes mellitus or cardiovascular disease. 6.2% only had type 2 diabetes mellitus, 28.1% only had cardiovascular disease and the remaining 9.4% had type 2 diabetes mellitus as well as cardiovascular disease. The overall SMRs were similar between parents whose medical health information was available and parents whose information was missing. Half of the parents who had died, i.e. 49.5%, had cardiovascular disease, whereas 34.9% of the parents who had not died had cardiovascular disease. First, we compared the mortality of the parents with the mortality of the general Dutch population, thereby evaluating whether having a daughter with PCOS would influence all-cause mortality. The overall life expectancy of the parents independent of their medical history was not influenced by the fact that their daughters were diagnosed with PCOS (SMR 1.04; 95% CI 0.98–1.12), nor was the life expectancy affected of mothers (SMR 1.13; 95% CI 0.93–1.37) and fathers (SMR 0.99; 95% CI 0.86–1.14) when analyzed separately. As predefined in the SMR method, data were also analyzed

Table I Baseline characteristics of the patients with PCOS.

<table>
<thead>
<tr>
<th></th>
<th>Included patients (n = 958)</th>
<th>Excluded patients (n = 130)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.7 (6.4)</td>
<td>27.5 (6.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 (9.0)</td>
<td>27.0 (9.0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>86 (23)</td>
<td>88 (22)</td>
<td>0.52</td>
</tr>
<tr>
<td>PCOM (n; %)</td>
<td>833; 90.1</td>
<td>105; 84.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Hyperandrogenism (n; %)</td>
<td>333; 55.6</td>
<td>73; 56.2</td>
<td>0.91</td>
</tr>
<tr>
<td>Amenorrhea (n; %)</td>
<td>264; 27.6</td>
<td>29; 22.3</td>
<td>0.25</td>
</tr>
<tr>
<td>OD + PCOM + HA</td>
<td>50.1%</td>
<td>46.0%</td>
<td>0.24</td>
</tr>
<tr>
<td>OD + PCOM</td>
<td>38.5%</td>
<td>37.3%</td>
<td></td>
</tr>
<tr>
<td>OD + HA</td>
<td>11.5%</td>
<td>16.9%</td>
<td></td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>4.6 (2.3)</td>
<td>4.3 (2.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>7.1 (5.9)</td>
<td>6.5 (6.3)</td>
<td>0.49</td>
</tr>
<tr>
<td>SHBG (mmol/l)</td>
<td>40.1 (36.3)</td>
<td>36.9 (30.5)</td>
<td>0.21</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>2.0 (1.3)</td>
<td>2.0 (1.3)</td>
<td>0.47</td>
</tr>
<tr>
<td>FAI</td>
<td>4.9 (5.4)</td>
<td>5.3 (5.4)</td>
<td>0.49</td>
</tr>
<tr>
<td>Androstenedione (nmol/l)</td>
<td>12.4 (6.8)</td>
<td>11.8 (7.6)</td>
<td>0.86</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.1 (0.8)</td>
<td>4.2 (0.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>71 (66)</td>
<td>72 (67)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Baseline characteristics are shown as median and interquartile ranges (IQR), unless indicated otherwise. BMI, body mass index; OD, ovulatory dysfunction; PCOM, polycystic ovarian morphology; HA, hyperandrogenism; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin; FAI, free androgen index.

aFor 39 patients (3.6%), ultrasound data were missing.

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As well as all-cause mortality: it has been postulated that patients with type 2 diabetes mellitus should be immediately treated as if they have had prior coronary disease (Haffner et al., 1998).

Over the last few decades, the prevalence of type 2 diabetes mellitus has started to increase in the Netherlands (Baan et al., 2009). Implementation of strict treatment guidelines and improvements in the quality of diabetes care in shared care settings have introduced a trend toward a mortality more similar to that of the general population (van Hateren et al., 2012). Nonetheless, we observed a 2-fold increased mortality in diabetic mothers of patients with PCOS relative to female patients with diabetes recruited from the general population. This excess mortality was not observed for the fathers compared with the male diabetic controls. Several studies have suggested that, unlike the general population, diabetic women have an even higher relative mortality rate than diabetic men (Becker et al., 2003; Booth et al., 2006; Huxley et al., 2006).

We did not observe large gender differences in mortality in our diabetic control population. The ZODIAC study is a prospective study that included patients treated for their type 2 diabetes in primary care and, except for those who were terminally ill, almost all patients were included in this cohort. The quality of diabetic care in this cohort seems well above average, and this might explain in part the higher relative mortality seen in women with diabetes in other cohorts (van Hateren et al., 2012). Different approaches to select cases and controls, i.e. cases by general practitioners versus academic hospitals and controls form the general population versus matched controls from a non-diabetic population, respectively, probably have contributed to ambiguous findings about gender and complications of type 2 diabetes. Nevertheless, it has been shown that surrogate markers for cardiovascular disease, such as elevated blood pressure, dyslipidemia and increased carotid intima-media thickness, are more prominently present in females than in males with diabetes (Juutilainen et al., 2004). These risk markers are also well-known co-morbidities of PCOS (Guzick et al., 1996; Ehrmann et al., 2006; Valkenburg et al., 2008). Although we did not assess the presence of PCOS in the post-menopausal mothers, previous studies have shown that mothers of PCOS patients do share clinical characteristics with their daughters in at least half of all cases. They suffer more often from irregular menstrual cycles and hirsutism compared with mothers with daughters without PCOS (Sam et al., 2006). Moreover, menstrual cycle irregularity, elevated androgen levels as well as the presence of diabetes predispose one to cardiovascular disease and events (Solomon et al.,

The familial and heritable nature of PCOS has been well established (Vink et al., 2006). Not only PCOS itself, but also associated co-morbidities of the syndrome evidently affect family members of patients with PCOS. Our findings support the notion that parents of patients diagnosed with PCOS develop type 2 diabetes mellitus more often than age-matched subjects in the general population (Ubink-Veltmaat et al., 2003).

### Discussion

Our study has shown that mothers above age 60 years with a daughter diagnosed with PCOS do have an increased mortality risk. Moreover, excess mortality was observed in mothers with type 2 diabetes mellitus, being twice as high as in female controls with diabetes.

The familial and heritable nature of PCOS has been well established (Vink et al., 2006). Not only PCOS itself, but also associated co-morbidities of the syndrome evidently affect family members of patients with PCOS. Our findings support the notion that parents of patients diagnosed with PCOS develop type 2 diabetes mellitus more often than age-matched subjects in the general population (Ubink-Veltmaat et al., 2003).

### Table II: Standardized mortality ratio of parents of patients with PCOS compared with the general Dutch population and of patients with diabetes compared with the general Dutch population.

<table>
<thead>
<tr>
<th></th>
<th>Person-years</th>
<th>Observed deaths (n)</th>
<th>Expected deaths (n)</th>
<th>SMR 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All parents</td>
<td>62 693.54</td>
<td>302</td>
<td>291.44</td>
<td>1.04</td>
<td>0.98-1.23</td>
</tr>
<tr>
<td>All mothers</td>
<td>32 785.34</td>
<td>106</td>
<td>93.69</td>
<td>1.13</td>
<td>0.93-1.37</td>
</tr>
<tr>
<td>All fathers</td>
<td>29 908.19</td>
<td>196</td>
<td>197.75</td>
<td>0.99</td>
<td>0.86-1.14</td>
</tr>
<tr>
<td>Mothers with type 2 diabetesa</td>
<td>3169.83</td>
<td>22</td>
<td>9.91</td>
<td>2.22</td>
<td>1.39-3.36</td>
</tr>
<tr>
<td>Fathers with type 2 diabetesa</td>
<td>3204.14</td>
<td>25</td>
<td>21.40</td>
<td>1.17</td>
<td>0.76-1.72</td>
</tr>
<tr>
<td>Female diabetic patientsb</td>
<td>6063.67</td>
<td>326</td>
<td>219.94</td>
<td>1.48</td>
<td>1.33-1.65</td>
</tr>
<tr>
<td>Male diabetic patientsb</td>
<td>4369.25</td>
<td>244</td>
<td>174.01</td>
<td>1.40</td>
<td>1.23-1.59</td>
</tr>
</tbody>
</table>

*a* Mothers and fathers diagnosed with type 2 diabetes mellitus and having a daughter diagnosed with PCOS.

*b* Females and males diagnosed with type 2 diabetes mellitus and recruited from a population-based cohort study.

n, number; SMR, standardized mortality ratio; CI, confidence interval.
patients with diabetes recruited from the general population suggests
the PCOS daughters. More importantly, the excess of mortality
ability of the syndrome, may serve as a warning for the future risk of
coming decades.

The presented reverse parent-offspring analysis overcomes the
problem of lacking adequate follow-up data and, because of high herit-
patients from the PCOM and hirsutism and/or hyperandrogenism but
patients will notice themselves. Therefore, if they do not have distressing

diagnosed as having PCOS, the most common endocrine disease in
women of reproductive age. Our study has a number of limitations.

We have investigated the link between reproductive risk factors and type 2 diabetes by selecting parents through a daughter with PCOS and control parents without selection based on PCOS. Current efforts to obtain end-point data based on large prospective follow-up studies of patients with PCOS and their family members will provide more profound insight in the coming decades.

The presented reverse parent-offspring analysis overcomes the
problem of lacking adequate follow-up data and, because of high herit-
ability of the syndrome, may serve as a warning for the future risk of
the PCOS daughters. More importantly, the excess of mortality observed in diabetic mothers of patients with PCOS relative to the
patients with diabetes recruited from the general population suggests
that this specific high-risk group is not sufficiently recognized, limiting
the use of preventive measures. Therefore, we feel that early and active screening as well as aggressive treatment for type 2 diabetes mellitus among these mothers of daughters suffering from PCOS is justified.

We realize that we observed a limited number of deaths. However, the
SMR method uses person-years and the corresponding population-
based expected deaths. Therefore, power problems hardly occur and
small numbers of deaths can be used to estimate differences with high
confidence as long as the number of person-years is large, which is the case in our study. The increased mortality of the mothers with type 2 diabetes mellitus is within the range caused by severe inherited cardiovascular disorders like familial hypercholesterolemia (Sjbrands et al., 2001). Early identification and treatment of cardiovascular risk factors may be
of major importance in this specific high-risk group, also in the light of the fact that the incidence of cardiovascular disease in women with diabetes begins to increase at least 15 years before diabetes is clinically diagnosed (Hu et al., 2002). Moreover, it is also known that type 2 diabetes is
much more common in patients with PCOS and ~20% of these patients develop diabetes as early as during their forth decade of life (Legro et al., 2005). In case of such a double burden, early diagnosis of diabetes will hopefully lead to early and aggressive treatment of risk factors, which in turn will have its effects on the primary outcome.

This is the first study observing this excess risk in parents of patients
diagnosed as having PCOS, the most common endocrine disease in
women of reproductive age. Our study has a number of limitations.

With the introduction of the Rotterdam criteria two additional pheno-
type groups were added to the PCOS phenotype: patients with oligo/
amenorrhea and PCOM and patients with hirsutism and/or hyperandro-
genism and PCOM. The presence of PCOM is usually not a symptom
patients will notice themselves. Therefore, if they do not have distressing
symptoms accompanying hyperandrogenism such as hirsutism or acne,
patients from the PCOM and hirsutism and/or hyperandrogenism but
ovulatory phenotype group are less likely to visit the outpatient clinic. This specific phenotype group is usually underrepresented in studies
including PCOS patients (Ezeh et al., 2013), as in the current study
population where it is completely absent. This may have influenced our study results.

One could argue that we excluded severe cases from the population-
based diabetic cohort. Excluding subjects with a very short life expect-
cy during the first months of a population-based cohort study is
accomplished to avoid effects of severe, prevalent diseases on the follow-
up of the cohort, limiting the observations to truly incident cases. If this
approach had introduced a bias, we would have expected excess mortal-
ity in the mothers below 60 years of age. However, this was not the case,
implying that type 2 diabetes mellitus is indeed a disease of the older
groups in our population. Questionnaires were used to get insight in the
co-morbidities of the parents, and unfortunately we did not get a
maximum response. Although this may have influenced our study, we
did not observe any differences in mortality rates between the parents of
the patients, who responded to the questionnaire, compared with those
who did not respond. The questionnaires may also have introduced recall bias for family history. Although recall bias for family
history was previously demonstrated to be minimal for long-term chronic diseases (Bensen et al., 1999) and the high prevalence of type 2 diabetes mellitus in the parents of our patients is in agreement with earlier studies (Sir-Petermann et al., 2002; Davies et al., 2011), the prevalence of diabetes in parents was based on their daughter’s self-report and

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**Figure 1** Standardized mortality ratio compared with the general population, number of deaths and person-years of mothers (A) and fathers (B) of patients with PCOS, divided by age categories. SMR, standardized mortality ratio; PYRS, person-years.

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2002; Krentz et al., 2007; Shaw et al., 2008).
was not clinically confirmed. This is a limitation of the study. We were not able to assess potential risk factors, including obesity, hypertension or dyslipidemia, in the studied parents, which might shed light on underlying biological mechanisms explaining the high mortality of the diabetic mothers. Future prospective follow-up studies are needed to identify these potential additional risk factors.

In conclusion, we observed excess mortality above the age of 60 years in mothers of patients with PCOS, most likely as a result of type 2 diabetes mellitus. Mothers with type 2 diabetes mellitus had a 2-fold excess mortality compared with females with diabetes recruited from the general population without selection on PCOS. Our findings justify screening for type 2 diabetes mellitus among the mothers with a daughter suffering from PCOS to ensure that good preventive and therapeutic measures according to the appropriate guidelines can be taken in a timely manner.

Authors’ roles
Y.V.L., E.J.G.S. and J.S.E.L. were involved in the study design. Y.V.L., M.E.R.-S., M.v.d.B., B.C.J.M.F., N.K., H.J.G.B. and J.S.E.L. participated in data collection. Y.V.L., M.E.R.-S. and E.J.G.S. performed the statistical analyses. All authors contributed in data interpretation. Y.V.L., M.E.R.-S., E.J.G.S. and J.S.E.L. participated in drafting and revising of the manuscript. Y.V.L., B.C.J.M.F., N.K., H.J.G.B. and M.v.d.B. contributed to the critical reading and editing of the manuscript. All authors approved the final version of the manuscript.

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Conflict of interest
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References


