The Impact of Obesity on the Incidence of Type 2 Diabetes Among Women With Polycystic Ovary Syndrome

Nadira S. Kakoly,[1] Arul Earnest,[1] Helena J. Teede,[1,2,3] Lisa J. Moran,[1] and Anju E. Joham[1,2]

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OBJECTIVE

The nature of the independent relationship between polycystic ovary syndrome (PCOS) and type 2 diabetes remains unclear. Few studies have aimed to clarify this relationship independent of obesity in longitudinal population-based cohorts.

RESEARCH DESIGN AND METHODS

We used the Australian Longitudinal Study on Women's Health (ALSWH) (2000–2015) database to estimate nationwide incidence rates and predictors of type 2 diabetes among women aged 18–42 using person-time and survival analysis.

RESULTS

Over a follow-up of 1,919 person-years (PYs), 186 women developed type 2 diabetes. The incidence rate was 4.19/1,000 PYs and 1.02/1,000 PYs ($P < 0.001$) in PCOS and control subjects. On subgroup analyses across healthy-weight, overweight, and obese categories of women, the incidence rates for type 2 diabetes were 3.21, 4.67, and 8.80, whereas incidence rate ratios were 4.68, 3.52, and 2.36 ($P < 0.005$) in PCOS versus age-matched control subjects. PCOS was one of the most influential predictors for type 2 diabetes in the entire cohort (hazard ratio 3.23, 95% CI 2.07–5.05, $P < 0.001$) adjusting for BMI, education, area of residence, and family history of type 2 diabetes.

CONCLUSIONS

Women with PCOS are at an increased risk of type 2 diabetes, irrespective of age and BMI. The incidence of type 2 diabetes increases substantially with increasing obesity; yet, PCOS adds a greater relative risk in lean women. Based on the overall moderate absolute clinical risk demonstrated here, guideline recommendations suggest type 2 diabetes screening every 1–3 years in all women with PCOS, across BMI categories and age ranges, with frequency influenced by additional type 2 diabetes risk factors.

Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by any two of the following three syndromes: oligoovulation/anovulation, clinical/biochemical hyperandrogenism, and polycystic ovaries on ultrasonogram. The syndrome is underpinned by hyperandrogenism and intrinsic insulin resistance (IR) (1) and can affect up to 18% women of reproductive age (2,3). PCOS has a range of metabolic features, including obesity (4), IR (5), gestational diabetes mellitus (6), and type 2 diabetes (7). Extrinsic or obesity-related IR (1) exacerbates the severity and metabolic features of the syndrome.

[1]Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Clayton, Victoria, Australia
[2]Diabetes and Vascular Medicine Unit, Monash Health, Clayton, Victoria, Australia
[3]Monash Partners Academic Health Science Centre, Melbourne, Victoria, Australia

Corresponding author: Anju E. Joham, anju.joham@monash.edu

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There is controversy surrounding the independent effect of PCOS on type 2 diabetes. Although some studies (7,8) suggest an effect of PCOS per se on type 2 diabetes, others propose this predominantly occurs in the context of obesity (9,10). Previous studies have been inconclusive about the independent effect of PCOS on type 2 diabetes, with methodological limitations including small sample sizes (8,9,11), use of convenience sampling, being performed in a clinical setting (10), cross-sectional in design (1,7), and non-/unmatched control groups (8,12). These limit the conclusions that can be drawn from the existing body of literature.

In this context, guideline recommendations on screening for impaired glucose tolerance (IGT) and type 2 diabetes vary considerably. In all consensus statements, including those of the Endocrine Society (13) and the Androgen Excess and Polycystic Ovary Syndrome Society (AE-PCOS) (14), as well as the evidence-based guidelines on PCOS diagnosis and management developed in Australia (15), screening for type 2 diabetes is recommended in PCOS. Some recommend screening in all women with PCOS, whereas others, including the European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM), target screening to women with PCOS with an additional risk factor such as increased BMI (>30 kg/m^2), increased age (>40 years), gestational diabetes mellitus, or a family history of type 2 diabetes. The American Diabetes Association (16), American College of Endocrinology (17), AE-PCOS (18), and the Australian guidelines recommend screening every 1–2 years in all women with PCOS and yearly among women with IGT or women who have significant additional risk factors.

There is a lack of appropriately powered and designed longitudinal studies (9,10), with few community-based cohorts, that have explored the relationships between PCOS, BMI, and type 2 diabetes to inform guidelines adequately. In particular, early identification of a high-risk group of women with PCOS predisposed to type 2 diabetes is constrained by a lack of data around incidence and time to type 2 diabetes, considering key factors such as BMI, weight gain over time, ethnicity, and familial predisposition for type 2 diabetes. This information is needed to inform guidelines and clinical practice internationally.

Given the current context of rising obesity among young adults and its implications for PCOS and type 2 diabetes, we aimed to assess the population-based incidence rate of type 2 diabetes among women with PCOS compared with women without, with a consideration of risk factors for type 2 diabetes with the objective of informing the new international PCOS guideline (19). We also aimed to clarify the role of PCOS independent of BMI on the development of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Data for this study were drawn from the Australian Longitudinal Study on Women's Health (ALSWH) database spanning 15 years, over seven surveys. The ALSWH is an ongoing longitudinal population-based cohort assessing the health of more than 58,000 Australian women. In 1996, the ALSWH first collected mailed survey data from three age cohorts of Australian women. The study initially randomly selected women from the national health insurance scheme (Medicare) database, which includes records of all permanent residents of Australia and is a community-recruited nationally representative population cohort. Further details of the methods used and sample characteristics were previously documented (6) and are available on the ALSWH website (http://www.alswh.org.au). The Human Research Ethics Committees of the University of Newcastle and the University of Queensland approved the study methods.

Women participating in the ALSWH from the 1973 to 1978 cohort (aged 18–42 years) were sent postal questionnaires every 3 years inquiring into their general health and well-being, including questions on PCOS, type 2 diabetes status, anthropometric and sociodemographic factors, and health behavior. Our analysis focused on seven waves of data collected in 1996, 2000, 2003, 2006, 2009, 2012, and 2015. The eligible sample, therefore, included all women from Survey II onward without any preexisting type 2 diabetes who responded to the PCOS questions (N = 8,378). Consistent with prior analysis in the ALSWH, this was taken as our baseline cohort.

The baseline cohort was subdivided into two groups: women who reported having been diagnosed with PCOS and women who did not report PCOS by 2015. At each survey time point, both of these cohorts were assessed to determine the number of women who did and did not develop type 2 diabetes and the numbers that were lost to follow-up. We examined data from these two cohorts for up to 15 years, from 2000 to 2015, for the development of new cases of type 2 diabetes.

Measures

Outcome: Type 2 Diabetes

In Surveys II–VII, women were asked: "In the last 3 years, have you been diagnosed or treated for type 2 diabetes?" Women who gave a positive response were classified as having type 2 diabetes (coded as a binary variable). For the purpose of this analysis, incident diabetes was defined as the first report of type 2 diabetes at a follow-up survey but not at the previous surveys, with the assumption of an enduring diagnosis of type 2 diabetes following that. The analysis excluded women who did not answer this question in any of the surveys. Type of diabetes was not specified at Survey I. Therefore, type 2 diabetes at Survey I was determined by correlating reports of type 2 diabetes at subsequent surveys (II–VII) with responses from Survey I (given that type 2 diabetes is enduring). We also reconfirmed that those women who were characterized as having type 2 diabetes at Survey I did not report type 1 diabetes in Surveys II–VII.

Independent Variable: PCOS

At Surveys IV–VII, women were asked: "In the last 3 years, have you been diagnosed or treated for PCOS?" Women who gave a positive response in any of the surveys were classified as having PCOS (coded as a binary variable). All other women were considered as not having PCOS. PCOS was also considered an enduring diagnosis, with women classified as having PCOS in Surveys IV–VII characterized as having PCOS at Surveys I–III. Women not answering this question in any of the four surveys (IV–VII) were not included in the PCOS analysis.

Confounders

BMI. BMI was calculated from self-reported height and weight and collected in all surveys. We used World Health Organization–defined categories

to classify women according to BMI (http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi, accessed on 31/01/2018). The categories were coded as follows: underweight, BMI <18.5 kg/m^2; healthy weight/lean, 18.5–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; and obese, ≥ 30.0 kg/m^2. We used BMI reported at Survey I as the baseline measure for this analysis.

Income. Women were asked to report their average household gross (before tax) income. Responses were categorized as $<$15,999, 16,000–51,999, and $\geq$52,000 Australian dollars per annum. We used Survey I responses for baseline difference in Table 1 and Survey VI responses as the current income for regression analysis.

Educational Qualification. Women were asked to report their highest educational qualification completed. Responses were categorized as "year 12 or less," "trade/certificate," and "university/higher-university degree." We used Survey I responses for the baseline difference in Table 1 and their highest qualification reported at Survey VII for the regression analysis.

Country of Birth. Country of birth responses were categorized as Australian, other English-speaking background (ESB) countries, European, Asian, or other countries, including Sub-Saharan Africa. Country of birth was used as a surrogate for ethnic affiliation. Countries of birth reported at Survey I was used for the study.

Occupation. The main occupation was assessed in all surveys. Women were asked what their main occupation was at the time of the survey. Responses were coded into four broad categories as "no paid job," "clerical/sales/service/production/transport worker/laborer," "associate professional/tradesperson/advanced clerical/service worker," and "professional/manager/administrator." We used Survey I responses for the baseline difference in Table 1 and the main occupation categories reported at Survey VII in regression analysis in Table 2.

Family History of Diabetes. At Survey VII, women were asked: "Do you have a family history of type 2 diabetes? (Blood relatives only)" which was used to identify women who had a familial risk for type 2 diabetes. This was coded as a binary variable.

Smoking. Women were asked about their smoking status. Categories were classified according to the World Health Organization (http://www.thl.fi/publications/ehrm/product1/section7.htm; accessed on 31/01/2018). These groups were then merged into three broad categories: nonsmoker, former smoker, and current smoker. We used Survey I responses for Table 1 and Survey VII responses for the regression analysis.

Outcome and Data Analysis

We used the χ^2 test or independent Student *t* test to examine the relationship between categorical and continuous variables with type 2 diabetes. The primary outcome of our study was the incidence of type 2 diabetes in women with PCOS. The incidence rate for women with PCOS overall (the number of cases of diabetes per 1,000 person-years [PYs]) and subgroups at high risk of type 2 diabetes (BMI, low income, education, family history of diabetes, smoking, hypertension, and country of birth at Survey I) were computed. The incidence rate ratio (IRR) for type 2 diabetes (defined as the incidence rate among women with PCOS over the incidence rate among women without PCOS) was calculated by BMI categories at Survey I. We also identified potential predictors of type 2 diabetes incidence using the Cox proportional hazards model.

Diabetes-free survival time was calculated from the year of entry into the study (2000) to the year of the event (first report of type 2 diabetes) or the end of follow-up (2015), whichever came first. Individuals with no event by the end of follow-up were censored. We fit an adjusted Cox regression model starting from all covariates significant at the 20% level in the univariate analysis for the multivariate analysis. A stepwise model with a probability of entry set at 1% and removal set at 5% was used to identify the final set of variables in the multivariate model. BMI subgroups at Survey I (healthy weight [BMI 18.5–24.9 kg/m^2]), overweight [BMI 25.0–29.9 kg/m^2], and obese [BMI $\geq$30 kg/m^2]) were evaluated for effect modification, and a subgroup analysis was performed. The Schoenfeld test was performed to check the validity of proportional hazards assumption. The overall fit of the regression models was assessed by examining the Cox-Snell residuals. Statistical significance was defined as a two-sided *P* value <0.05 for all analyses. All analyses were performed using Stata 13.0 software (StataCorp, College Station, TX).

RESULTS

Study Sample

Overall, 9,688 women returned responses to Survey II. We excluded 19 women who were classified as having preexisting type 2 diabetes, leaving 9,669 women free of preexisting type 2 diabetes. Among these, 8,378 participants answered the PCOS question and formed our baseline cohort. For this analysis, we divided these women into two further cohorts: PCOS (*n* = 707) and non-PCOS (*n* = 7,671). We examined data from these two cohorts to determine the proportion of women who developed type 2 diabetes by Survey VII (2015).

Baseline Characteristics of Study Population With and Without Type 2 Diabetes

The baseline characteristics of the sample are presented in Table 1. At baseline, women who did and did not develop type 2 diabetes were comparable with regard to yearly household income, history of smoking and hypertension, age, and ethnic classification. However, women who developed type 2 diabetes were more likely to have PCOS, be overweight/obese, and have a family history of type 2 diabetes (Table 1).

Type 2 Diabetes Event Rates

The mean follow-up duration was 15 years from Survey II onwards. The incidence rate of type 2 diabetes was 1.28 cases/1,000 PYs in the entire cohort. The mean incidence in the PCOS cohort was 4.19/1,000 PYs (95% CI 3.18–5.51) compared with 1.02/1,000 PYs (95% CI 0.86–1.20) ($P < 0.001$) among women not reporting PCOS. Among women with PCOS, the mean incidence of type 2 diabetes differed by BMI, education, income, smoking, occupation, the area of residence, and ethnicity. The incidence rates of type 2 diabetes by baseline healthy-weight, overweight, and obese women at Survey I with PCOS were 3.21, 4.67, and 8.80/1,000 PYs,

Table 1—Baseline characteristics of the study sample by status of diabetes

Characteristics	Incident type 2 diabetes		*P* value*
	No (*N* = 8,192)	Yes (*N* = 186)	
PCOS			
No	7,536 (91.99)	135 (72.58)	**<0.001**
Yes	656 (8.01)	51 (27.42)	
BMI classification (kg/m^2)			
Underweight, BMI <18.5	670 (9.29)	9 (5.77)	
Healthy weight, BMI 18.5 to <25.0	5,024 (69.63)	77 (49.36)	**<0.001**
Overweight, BMI 25.0 to <30.0	1,096 (15.19)	33 (21.15)	
Obese, BMI ≥30.0	425 (5.89)	37 (23.72)	
Household gross yearly income ($AUD)			
≤15,999	257 (3.76)	8 (5.33)	0.54
16,000–51,999	2,541 (37.18)	52 (34.67)	
≥52,000	4,036 (59.06)	90 (60.00)	
Hypertension other than pregnancy			
No	7,901 (97.36)	177 (96.72)	0.59
Yes	214 (2.64)	6 (3.28)	
Smoking status			
Nonsmoker	4,485 (56.98)	92 (50.27)	0.16
Former smoker	1,171 (14.88)	34 (18.58)	
Current smoker	2,215 (28.14)	57 (31.15)	
Family history of type 2 diabetes			
No	4,250 (74.85)	68 (51.52)	**<0.001**
Yes	1,428 (25.15)	64 (48.48)	
Age, mean (SD), years	24.59 (1.47)	24.65 (1.49)	0.59
Education			
Year 12 or less	5,632 (69.03)	120 (66.30)	**0.007**
Trade/certificate	1,434 (17.58)	46 (25.41)	
University/higher university degree	1,093 (13.40)	15 (8.29)	
Ethnicity			
Australian born	7,586 (93.22)	167 (89.78)	
Other ESB	283 (3.48)	9 (4.84)	0.053
Europe	73 (0.90)	0 (0.00)	
Asia	136 (1.67)	7 (3.76)	
Others (Sub-Saharan Africa)	60 (0.74)	3 (1.61)	
Occupation			
No paid job	563 (6.97)	21 (11.60)	
Clerical/sales/service/production/transport worker/ laborer	3,352 (41.48)	89 (49.17)	**0.004**
Assoc. professional/tradesperson/service worker	645 (7.98)	13 (7.18)	
Professional/manager/administration	3,521 (43.57)	58 (32.04)	

Data are presented as *n* (%) or as indicated otherwise. Bold *P* values are statistically significant ($P \leq 0.05$). AUS, Australian dollars. *The χ^2 test for categorical variables and *t* test for continuous variables were used to test for difference between the two groups.

respectively. The incidence rates among women born in Australia, other English-speaking countries (U.S. and South Africa), and Asia were 4.11, 6.12, and 9.35/1,000 PYs, respectively (Supplementary Table 1).

Kaplan-Meier Survival Curve

The Kaplan-Meier survival curves for the length of time after enrollment until the occurrence of type 2 diabetes (incident type 2 diabetes) are presented for the PCOS and non-PCOS groups (Fig. 1). There was a significant difference in type 2 diabetes-free survival times between the groups (log-rank test $P < 0.001$). The Kaplan-Meier survival probability estimates at 15 years were 0.952 for PCOS and 0.988 for the non-PCOS group.

Subgroup Analyses

When stratified by class of BMI at Survey I, women in all BMI subgroups (healthy weight, overweight, and obese) had an increased incidence of type 2 diabetes among women with PCOS compared with women without. The incidence rate increased in both women with (3.21, 4.67, 8.80) and without PCOS (0.69, 1.33, 3.72) by class of BMI, including healthy-weight, overweight, and obese women, respectively (Fig. 2). Compared with overweight and obese subgroups, healthy-weight women with PCOS had the highest IRR (4.68 vs. 3.52 vs. 2.36) (Table 3).

Regression Analysis

Among eight variables (family history of type 2 diabetes, PCOS, BMI, education, ethnicity, smoking, area of residence, and occupation) that were associated ($P \leq 0.2$) with type 2 diabetes on univariate analysis and subsequently entered into the multivariable model, only five remained as independent predictors (BMI, education, family history of

Table 2—Cox regression models: crude and adjusted HRs of baseline characteristics predicting the development of type 2 diabetes

	Univariate			Multivariate		
Characteristics	HR	95% CI	*P* value	HR	95% CI	*P* value
PCOS (ref non-PCOS)*	4.13	2.99–5.70	<0.001	3.23	2.07–5.05	<0.001
Age at Survey I	1.03	0.93–1.14	0.576			
Family history of type 2 diabetes*	2.75	1.95–3.86	<0.001	2.27	1.54–3.36	<0.001
Gross household income (ref ≤15,999 AUD)						
16,000–51,999	1.36	0.88–2.11	0.164			
≥52,000	0.77	0.47–1.25	0.288			
BMI (ref healthy weight)*						
Underweight, BMI <18.5 kg/m^2	0.96	0.50–1.86	0.907	0.95	0.41–2.22	0.908
Overweight, 25.0–24.9 kg/m^2	1.94	1.29–2.92	0.001	1.86	1.15–3.01	0.011
Obese, ≥30 kg/m^2	5.66	3.84–8.34	<0.001	2.80	1.63–4.93	<0.001
Education (ref year 12 or less)*						
Trade/apprenticeship	0.84	0.53–1.32	0.444	0.85	0.51–1.41	0.519
University/higher university	0.40	0.26–0.63	<0.001	0.41	0.25–0.69	0.001
Smoking (ref nonsmoker)*						
Former smoker	1.24	0.84–1.82	0.279			
Current smoker	1.76	1.07–2.88	0.025			
Ethnicity (ref Australian)*						
Other ESB	1.42	0.73–2.78	0.334	1.35	0.55–3.33	0.518
Europe	NC			NC		
Asia	2.43	1.14–5.19	0.021	5.11	2.04–12.79	0.001
Others	2.25	0.72–7.05	0.164	2.01	0.28–14.58	0.488
Occupation (ref no paid job)*						
Clerical/sales/service/production/transport	0.70	0.43–1.13	0.141			
Assoc. professional/tradesperson/advanced clerical/service worker	0.52	0.26–1.04	0.066			
Professional/manager/administration	0.41	0.25–0.68	0.001			
Area of residence Survey VII (ref major cities of Australia)						
Inner regional Australia	1.17	0.78–1.75	0.451			
Outer regional Australia	1.67	1.05–2.66	0.031			
Remote Australia	1.93	0.70–5.28	0.203			
Very remote Australia	1.36	0.19–9.80	0.760			

Each variable adjusted for all other variables. AUD, Australian dollars; NC, not computable. *Variables entered into the multivariate Cox regression model.

type 2 diabetes, ethnicity, and PCOS). After adjusting for family history of type 2 diabetes, BMI, ethnicity, and education, women with PCOS had a 3.23-fold increased risk of type 2 diabetes compared with women without PCOS (adjusted hazard ratio [HR] 3.23, 95% CI 2.07–5.05). Family history of type 2 diabetes, overweight and obesity, university/higher university education, and being of Asian birth versus of Australian birth (as a surrogate for ethnicity) also independently increased the risk for type 2 diabetes, adjusting for PCOS and other covariables (Table 2). There was no statistically significant evidence that the risk for type 2 diabetes differed between those born in Australia and any of the other examined regions of birth. We also looked at the PCOS and BMI interaction for the outcome of incident type 2 diabetes but observed no statistically significant association (P = 0.352) for the interaction.

CONCLUSIONS

This is one of the few nationally representative population-based longitudinal studies to report the incidence of type 2 diabetes among women with PCOS compared with women without PCOS. This Australian study extended over a 15-year period in women aged 18–42 years and showed an increased incidence of type 2 diabetes among women with PCOS compared with women without PCOS. Moreover, this risk was sustained across all BMI categories (healthy weight, overweight, and obese), with the highest IRR, reflecting the effect of PCOS status, noted in those of healthy weight. On regression analysis, PCOS status independently increased type 2 diabetes incidence among young adult women with PCOS. After adjusting for BMI, education, country of birth, area of residence, and family history of type 2 diabetes, the risk was 3.23-fold with PCOS.

Our current study found a self-reported incidence of type 2 diabetes of ~4/1,000 PYs in women with PCOS (~0.5% per year). Previous literature has reported type 2 diabetes incidence ranging between 6 and 22/1,000 PYs (10,20,21), in mostly clinic-based samples with likely more severe PCOS phenotypes and with a shorter follow-up. There are few longitudinal population-based data sets available for analysis for risk of type 2 diabetes in PCOS (7). Our results indicate a substantially higher incidence of type 2 diabetes in women with PCOS compared with women without PCOS, which confirms and underscores the importance of screening for type 2 diabetes in this population.

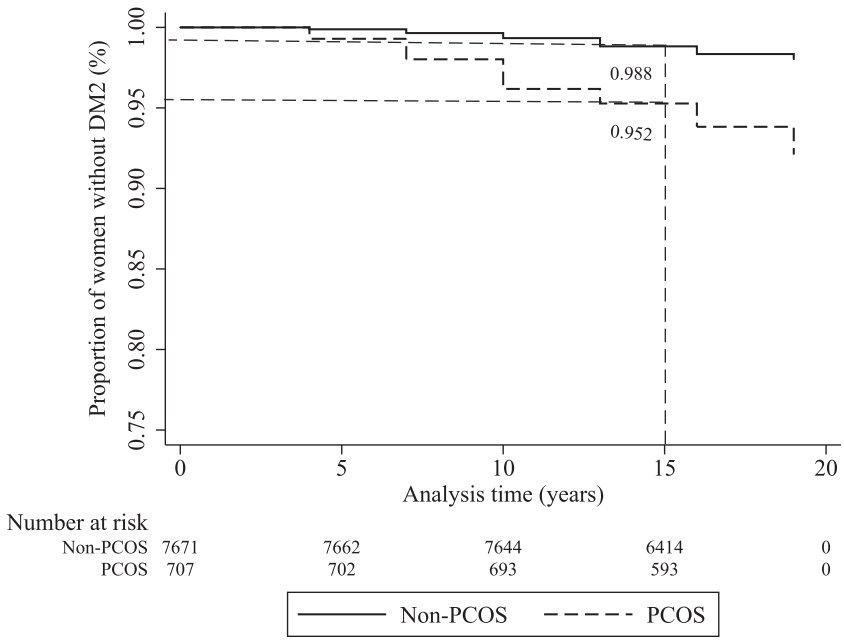

Figure 1—Kaplan-Meier survival curves for the length of time after enrollment until the occurrence of type 2 diabetes (DM2) for the PCOS and non-PCOS groups.

The relatively modest annual incidence among women with PCOS shown here may be related to the underreporting in a self-reported study. The reported type 2 diabetes incidence in PCOS of 4–22/1,000 PYs would align with the risk reported for the general population, identified as high risk at age 45 years and older, where the incidence is 7–21/1,000 PYs. In this group, screening was recommended every 1–3 years (15). In the current study containing younger women with PCOS (18–42 years), the risks are similar, providing a strong rationale for type 2 diabetes screening in the PCOS population from a young age.

As expected, the incidence of type 2 diabetes varied by BMI. Prior studies have shown an independent and additive effect of excess adiposity for women with PCOS (7,9), whereas others suggest type 2 diabetes in PCOS is primarily attributable to obesity (12). Our results indicate a significant increase in the risk of type 2 diabetes among women with PCOS independent of BMI and show this risk to be present in all BMI categories, with the IRR being strongest in the healthy-weight subgroup. Our findings are in contrast with a Finnish study (22) of 1,856 women from a population-based birth cohort. They reported that the risk of type 2 diabetes in women with PCOS was mainly attributable to obesity (odds ratio [OR] 2.45, 95% CI 1.28–4.67), with healthy-weight women with PCOS not at increased risk of type 2 diabetes (OR 1.10, 95% CI 0.31–3.80). Their findings are consistent with the international literature showing a milder metabolic phenotype in women with PCOS from northern Europe (23). It may also be attributed to the small number of healthy-weight subjects with PCOS in the Finnish study, with none who developed type 2 diabetes (healthy weight 0/62 [case subjects] vs. 20/358 [control subjects]). In Australia, if screening occurred every 3 years in women with PCOS aged 18–42, with incidence rates of type 2 diabetes assumed to remain relatively constant over this time, then the cumulative incidence for these 3 years would be 9.63, 14.01, and 26.4/1,000 PYs or ~1%, 1.4%, and 2.6%, respectively, in healthy-weight, overweight, and obese women with PCOS. Taken together, screening across the BMI range in PCOS with simple, inexpensive, and readily available blood tests (fasting glucose, HbA_{1c}, and oral glucose tolerance tests) would appear justified, pending cost-effectiveness analyses.

Here, the incidence of type 2 diabetes in Australian-born women with PCOS who are primarily from Caucasian backgrounds was 3.23 times higher than that of the general female population aged 18–42 years. Our findings are consistent with meta-analyses (8) and smaller hospital-based studies (8,21,24). Moreover, we found PCOS was one of the most influential predictors of type 2 diabetes development by the age of 42 (OR 3.23, 95% CI 2.07–5.05), with PCOS status identified as an independent predictor after adjusting for family history of type 2 diabetes, BMI, ethnicity, and education. Our current understanding of PCOS is as a condition characterized by defects in insulin secretion as well as insulin action, with PCOS thought to be an enduring disorder with manifestations beginning in adolescence. Type 2 diabetes in the general population increases as a person ages (beyond 40 years), and because ours is still a relatively young cohort, the full

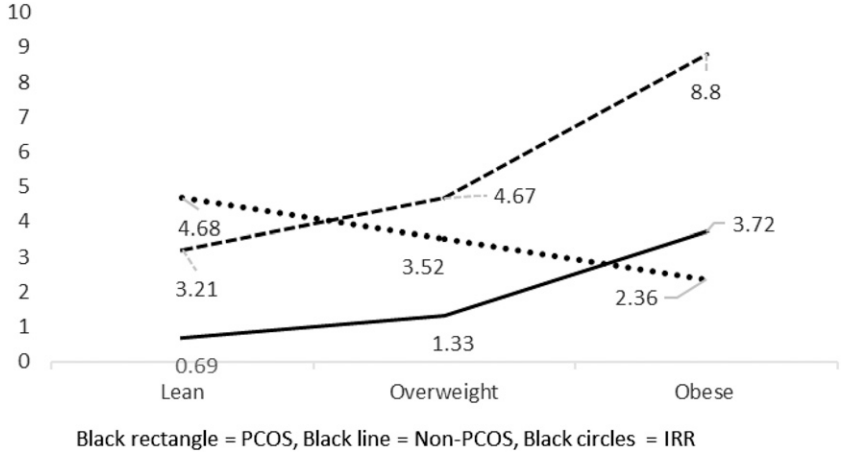

Figure 2—The incidence rate of type 2 diabetes in women with and without PCOS by class of BMI, including healthy weight/lean, overweight, and obese.

Table 3—Incidence rate and IRR among women with and without PCOS by BMI categories

	PCOS		Non-PCOS		
Subgroup	*n*/PYs	IR (95% CI)	*n*/PYs	IR (95% CI)	IRR (95% CI)
Lean	20/6,226	3.21 (2.07–4.98)	57/83,031	0.69 (0.53–0.89)	4.68 (2.66–7.91)
Overweight	10/2,141	4.67 (2.51–8.68)	23/17,330	1.33 (0.89–2.00)	3.52 (1.50–7.69)
Obese	14/1,591	8.80 (5.21–14.86)	23/6,176	3.72 (2.47–5.60)	2.36 (1.12–4.79)

IR, incidence rate; *n*, number of participants.

metabolic expression of PCOS may not yet be apparent. Despite this, we observed clear differences in the incidence of type 2 diabetes among women with PCOS versus women without PCOS (Kaplan-Meier survival curve) during the peak reproductive years. In women of reproductive age, IGT and type 2 diabetes contribute to significant maternal and neonatal morbidity, supporting the public health argument for screening in young women with PCOS. Considerations for screening also need to acknowledge the benefits of identification of IGT and effective prevention opportunities, including metformin and lifestyle intervention (25). In this context, we propose this evidence strongly supports screening for IGT and type 2 diabetes from young adulthood in PCOS.

The main strengths of our study include the large, unselected community cohort with excellent retention over time and the ability to adjust for important confounders. Our population database arose from an ongoing national registry, characterized as an open cohort with women able to move to other residential addresses. We propose that our use of the incidence rate as a measure of disease progression is better than cumulative incidence applied in previous studies. The cohort is compared with the most recent national census data to ensure representativeness is maintained and to quantify biases. These show participants to be representative of the general population of Australia, underscoring the generalizability of our findings (26).

Limitations include the use of self-reported measures of BMI, PCOS, and type 2 diabetes, and we acknowledge the bias that will be inherent in the use of self-reported measures. However, self-reported measures of PCOS have been validated with menstrual irregularity in this cohort (27), and self-reported BMI has been validated with direct anthropometric measurement among the middle-aged ALSWH cohort (28). Furthermore, the self-reported measure of type 2 diabetes used in this study was found to be a reliable proxy for medical record review in the U.S. and supports the use of self-reported diabetes as a valid outcome for observational studies (29). We do not have access to data on prediabetes or HbA_{1c} to validate our findings within this cohort.

A second limitation is that we do not know the specific timing of PCOS and the type 2 diabetes diagnosis between surveys or the specific diagnostic criteria physicians used for the diagnoses. However, this should not influence the incidence rates reported because these gaps in time have been taken as single time points and are similar for PCOS, type 2 diabetes, and all other variables in the survey. Moreover, although there may have been a degree of inconsistency in the criteria used for diagnosis of PCOS or type 2 diabetes, because these were all physician-diagnosed cases with likely laboratory investigations, the classification of cases should be valid.

Finally, given the association between PCOS and type 2 diabetes, it is possible that women with PCOS could have been screened more frequently than control women without PCOS. However, a recent cross-sectional study (30) reports a high proportion of type 2 diabetes cases (9.7%) among previously undiagnosed PCOS patients, suggesting that the increased prevalence is not due to observational (frequency of screening) bias. Hence, it is unlikely that the IRR observed in our study is solely a result of screening/observational bias. Given the low level of awareness of diabetes risk related to PCOS and potential underdiagnosis of both PCOS and type 2 diabetes, our findings may underestimate diabetes risk. Optimally, direct clinical and biochemical assessment and screening of this cohort with PCOS and matched controls is an essential next step.

Taken together, our findings indicate that PCOS is independently associated with an increased incidence of type 2 diabetes among young Australian-born women and that this increased risk is present in all BMI categories and across all age ranges. Based on the moderate absolute clinical risk demonstrated here, guideline recommendations should consider type 2 diabetes screening in all women with PCOS at least every 3 years from early adulthood, depending on local resources and patient preference. Our findings have informed the new international guidelines by highlighting the absolute clinical incidence of type 2 diabetes and confirmed the need for screening all women with PCOS.

We support the consensus statements by the Endocrine Society (13), the AE-PCOS (14), the Australian Evidence-Based Guidelines, and the new international PCOS guidelines (19) by demonstrating a moderate absolute clinical risk, and our data align with current population recommendations for screening every 3 years for those at high risk of type 2 diabetes. Recommendations will also need to be informed by future cost-effectiveness studies on screening.

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