Incidence And Prevalence Of Diabetes And Cost Of Illness Analysis Of Polycystic Ovary Syndrome: A Bayesian Modelling Study

Short title: Bayesian modelling for PCOS and diabetes

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Abstract

Study question: What is the incidence/prevalence of type 2 diabetes in women with polycystic ovary syndrome (PCOS) and the economic burden associated with PCOS in the UK?

Summary answer: The incidence and prevalence of type 2 diabetes in women with PCOS are 3-33 per 1000 person years and 26.5%, respectively, with an associated annual healthcare burden of at least £237 million in the UK.

What is known already: Although observational studies have been designed to assess the incidence of diabetes in women with PCOS, these have beenopen to criticism because of short periods of follow-up, small sample sizes or invalidated diagnosis of PCOS. Only one study has estimated the healthcare-related economic burden of PCOS, reporting a cost of $4.36 billion per year in the USA.

Study design, size, duration: This was a modelling study using individual patient data from a UK primary care database between 2004 and 2014 and aggregate data from the literature to obtain conversion rates through disease progression of PCOS. A simulation approach was applied to model the population dynamics of PCOS over a follow-up period of 25 years.

Participants/materials, setting, methods: A total of 14,135 women with PCOS or symptoms indicative of PCOS were selected from the primary care database to estimate the incidence of confirmed diagnosis of PCOS and diagnosis of type 2 diabetes. A “virtual’’ cohort including the entire PCOS population (size estimated from the UK census data) was simulated to model the population dynamics of PCOS. The economic and utility analyses were further conducted from a healthcare perspective.

Main results and the role of chance: The peak conversion rate from possible to diagnosed PCOS was 121 per 1000 person-year (PY). The maximal incidence of type 2 diabetes was 33 per 1000 PY. The estimated prevalence of diabetes in the PCOS population was 26.5% (95% interval: 25.4%-27.8%) during a 25-year follow-up. The annual healthcare burden of PCOS based on our conservative estimate is at least £237 million for the follow-up period examined.

Limitations, reasons for caution: Due to lack of data, a full economic evaluation including healthcare costs of all the comorbidities associated with PCOS was not possible. Simplification of the real-world situation represented by the model may be a concern.

Wider implications of the findings: This study suggests that a large number of women with symptoms indicative of PCOS never receive a definitive diagnosis yet can suffer from a rapid conversion to diabetes. This significantly reduces the quality of life for individual patients and incurs high costs for healthcare providers. As the risk of diabetes in women with PCOS is similar to that seen in populations at high risks of diabetes, it is possible that including them in national screening programmes may be cost effective.

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Trial registration number: Not applicable

Key words: PCOS / incidence / cost / diabetes / Bayesian modelling

Introduction

Polycystic ovary syndrome (PCOS) was originally considered a reproductive endocrine condition but it is now recognised as a multi-system disorder associated with type 2 diabetes, coronary heart disease, stroke, and endometrial cancer (Anderson et al., 2014; Barry et al., 2014; Morgan et al., 2012). Because its aetiology is unknown and the symptoms are so diverse, a wide range of treatments are used, with most of them exclusively directed at symptoms (Ding et al., 2016). Although the association with diabetes was first reported in 1980 (Burghen et al., 1980), the impact of PCOS on individuals and healthcare providers is still largely underestimated. Community studies have indicated that PCOS is a common endocrine disorder in women, with an estimated prevalence of 4.8-8% in the white population (Diamanti-Kandarakis et al., 1999; Asuncion et al., 2000; Sanchon et al., 2012; Lauritsen et al., 2014). Given its high prevalence and the associated long-term morbidities, the healthcare costs of PCOS are likely to be considerable. However, as far as we are aware there has been only one published cost-of-illness study, showing that the total cost for investigation and treatment for reproductive-aged women with PCOS in the USA is $4.36 billion per year, with treatment of type 2 diabetes accounting for over 40% of the costs (Azziz et al., 2005).

In this study, we modelled the population dynamics of PCOS to estimate the prevalence of type 2 diabetes in PCOS population. We also estimated the healthcare costs and quality of life associated with PCOS in the UK over the course of a 25-year period, from 2014 to 2039, using a simulation-based approach.

Methods

Data source

We used a combination of data sources to fully address our research questions. Individual patient data were extracted from The Health Improvement Network (THIN), a primary care database in the UK with patient data collected from more than 500 practices, covering over 6% of the patient population in England and Wales. Aggregate data from other sources include published observational studies (selected through a systematic search), UK census data and lifetable from the Office for National Statistics (Office for National Statistics), the British National Formulary (BNF) (Joint Formulary Committee, 2015) and published reports by the National Health Service (NHS).

Ethical approval

No approval was required for this study.

Study population

A cohort of women with PCOS were selected from THIN, from which we estimated several parameters of interest. This cohort consisted of women aged 15-44 who permanently have registered and contributed at least one year of data to THIN, with a diagnosis of PCOS or two or more symptoms indicative of PCOS (e.g. menstrual irregularities, hyperandrogenism, polycystic ovaries) (Ding et al., 2016). We only included data from practices that were deemed to use their computer system fully to record patient consultations (e.g. at least one medical record, one additional health data record such as body mass index and two therapy records per patient are computerised each year for a practice) and had acceptable mortality reporting (Horsfall et al., 2013; Maguire et al., 2009). We then simulated a 'virtual'

population including the entire PCOS cohort in the UK, whose size was estimated from the UK census data.

Modelling approach

The analysis was mainly based on a multistate model, which is often called a Markov model (MM) in health economic evaluation (Briggs and Sculpher, 1998). We assumed that the progression of PCOS consists of four possible states: probable PCOS (State 1), diagnosed PCOS (State 2), PCOS with diabetes (State 3) and death (State 4). Figure 1 graphically represents the MM and the definition for each state as follows. State 1: Women who present symptoms indicative of PCOS but have not yet received a confirmed diagnosis. State 2: Women who have been clinically diagnosed with PCOS. This group consists of prevalent cases and newly emerging cases each year. State 3: PCOS patients who have developed type 2 diabetes. Once patients enter this state, we assumed that they cannot be cured and will either remain or die (State 4). State 4: This is an "irreversible" state, because obviously individuals who transit here cannot move away.

The movements are governed by suitable transition probabilities, represented by the parameters $□_{12}, □_{13}, □_{14}, □_{23}, □_{24}, □_{34}$ (Figure 1), where the notation $□_{□□}$ ($□, □ = 1,2,3,4$ here to represent different states) indicates the probability that a random individual in the population moves between state □ and state □ betweenyear □ and year $□ + 1$ of the follow-up (Supplementary Table I).

The transition probabilities describing the movements across the disease states (State 1, 2 and 3) were estimated using a Poisson regression model controlled for age and framed in a

Bayesian setting. The full model specification and assumptions are presented in Supplementary Information.

The analysis was performed using JAGS (Hornik et al., 2003) interfaced with R. Two Markov chains running simultaneously and a total of 50,000 simulations per chain were generated, with the first 5,000 in the burn-in (pre-convergence) period discarded. In order to reduce autocorrelation, we then thinned the chains by including in our analysis 1 every 90. This resulted in estimates being based on 1,000 independent simulations. The model convergence was assessed based on the Gelman-Rubin diagnostic statistics (see more details in Supplementary), which were provided for all parameters in the model (Supplementary Figure I, II and III).

As the Poisson regression estimated the instantaneous rates, we converted these incidence rates into annual transition probabilities for the MM by assuming that the incidence rates were constant for a given age group during a Markov cycle of 1 year.

The baseline year was set to be 2014, with a follow-up of 25 years. The rationale for the selection of the time horizon and the assumptions for simulation are discussed in Supplementary Information. Two scenarios were considered and simulated: (i) a closed cohort with PCOS population aged 15-44; and (ii) an open cohort model with females aged 1-14 in 2014 gradually entering the study population in the follow-up period.

Quality of life and costs analysis

The healthcare costs of PCOS and type 2 diabetes was projected by summing the cost of each relevant treatment. The overall cost of an individual treatment was estimated by

multiplying its unit cost, daily dose and treatment duration by the number of patients requiring that treatment in a given state at a given time.

The unit cost of the drugs considered was based on the listing prices reported in the BNF and published studies. The healthcare costs for individual PCOS patients with diabetes were approximated by that of diabetic patients (Hex et al., 2012). Since it is difficult to quantify the costs of lifestyle modification, we only considered costs of all the relevant drugs. The summary of the drug doses and costs are displayed in Table 1.

The cumulative proportion of PCOS patients receiving the most relevant prescriptions for the condition at least once within one year after the diagnosis was estimated using data from THIN (Supplementary Table II). The recommended dose of each treatment considered were referred from the BNF and experts interviews (Supplementary Table III).

Quality of life (QoL) data from published studies were used for estimation. We assumed that probable cases have the same QoL as diagnosed cases (Coffey et al., 2006) as many probable cases may indeed be true cases but remain under-diagnosed due to failure of screening. The QoL of PCOS patients who developed diabetes was approximated by that of diabetic patients (Jhita et al., 2014) because, at present, there is no study providing data for this specific cohort. To facilitate the comparisons across economic evaluations (National Institute for Health and Clinical Excellence, 2013), we converted the QoL estimates for PCOS patients using the 36-Item short survey form (SF-36) into EQ-5D score (Ara and Brazier, 2008). The QoL of a virtual healthy cohort of the same population size as the PCOS cohort was simulated in comparison with our PCOS cohort and the QoL of the general population in the UK was referred from Kind et al. (Kind et al., 1999)

As is recommended in health economic evaluations, discounting can adjust future costs and outcomes of healthcare interventions to their "present value''. Therefore, the discounting rate in the UK (i.e. 3.5%) was applied (National Institute for Health and Clinical Excellence, 2013) to both costs and QoL measures.

Sensitivity analysis

We included analysis for "what-if" scenarios, i.e. the impact of varying incidence rates based on different assumptions (estimates for transition from diagnosed PCOS to diabetes) for the Poisson regression model on the proportion of patients ending up in diabetic state in the MM. The details of these "what-if" scenarios are presented in the Supplementary Information.

Results

Data sharing

Model output data are available on request from Tao Ding. More information of current on-going projects in our research group can be found:
http://www.ucl.ac.uk/statistics/research/statistics-health-economics/current-projects

Incidence rates of PCOS and diabetes in women with PCOS

The incidence rates for probable cases to receive a diagnosis of PCOS vary for different age groups and are notably lower for older women: above 100 per 1000 PY for women aged 15-19 and below 20 per 1000 PY for women aged 30 and above (Table 2).

The estimated incidence rates of probable cases converting to diabetes are also presented in Table 2 and younger women are associated with higher rates. The estimated incidence rates of diagnosed cases converting to diabetes do not vary substantially for different age groups in the base case scenario, remaining constant between 22 and 32 per 1000 PY. After including assumptions based on empirical studies (Sensitivity analysis 1 and 2), variation was observed for different age groups, e.g. the incidence rate of diabetes is below 5 per 1000 PY for women aged 15-19 and increases to 30 per 1000 for women aged 40-44 years.

Cohort simulation

The UK census data suggest a total number of 17,793,085 women aged 1-44 in 2014. The closed and open cohort model included 287,888 and 318,235 PCOS patients, respectively, for simulations. Table 3 shows the age distribution of PCOS patients.

The projected number of patients over states at consecutive 5-year intervals after 2014 is displayed in Table 4. The closed cohort model estimated that 26.3% (95% interval: 25.2%-27.6%) of the PCOS patients are likely to convert to diabetes by the end of follow-up and the proportion is 26.5% (95% interval: 25.4%-27.8%) for the open cohort model. The distribution of patients over states is displayed in the rainbow plots (Figure 2).

Healthcare-related economic burden

The estimated healthcare cost of PCOS is approximately £237 million (95% interval: £237-238 million) in 2014 and it increases over the follow-up period (Figure 3), with a present value of the overall disease burden of over £7 billion (95% interval: £6.8-7.3 billion) after applying discounting. The mean costs per patient per year are within a range of £723-950 during the 25-year follow-up (e.g. £723 in 2014, increased to a discounted value of £950 in 2023). This corresponds to an overall mean cost for an individual patient on an annual basis of £876 during the entire follow-up period. The costs of treating diabetes account for over 96% of the overall healthcare burden.

Quality of life

The mean score of EQ-5D is 0.76 and 0.7 (SD 0.3) for PCOS patients and PCOS patients with diabetes, respectively. Over the 25-year follow-up, the QoL is reduced from 0.75 (95% interval: 0.67-0.79) to 0.31 (95% interval: 0.24-0.34) for the entire cohort simulated. This is lower compared to the healthy cohort (from 0.85 in 2014 to 0.35 in 2039), as represented by the shaded area in grey (Figure 4).

Discussion

Summary

We modelled the population dynamics of PCOS, healthcare costs and QoL for women who developed PCOS in the UK from 2014 to 2039. The results suggest that 26% of PCOS population may develop diabetes by the end of follow-up, and this remained robust in the sensitivity analysis. The QoL of PCOS patients was lower than women without PCOS (quality

deficits of 0.04-0.1) throughout the follow-up period. The cost to the NHS was estimated to be at least £237 million per year.

Strengths and limitations

As far as we are aware, this is the first study to combine a large cohort of women, with validation of the diagnosis of PCOS and long follow-up, to report the annual incidence of PCOS. It is also the first health economic evaluation of this condition in a European population and the first analysis to model the QoL using a general (non-clinic) population. We applied a modelling approach to the real-world evidence, which is a cost-effective way to explore what-if scenarios using simulations for a long follow-up period. Modelling, however has inherent limitations so we accept the need to corroborate our results using the international prospective ongoing databases which are currently being developed. The data used in this study was derived from THIN which is a database of UK patients so the risks of diabetes that we found might differ from other countries depending on various factors including rates of obesity.

As we used individual patient data (IPD) from routine practices, the estimated transition rates reflect the true conversion between disease states for the referred PCOS population because most of the patients' experience are within the primary care in the UK. However, patients with more severe symptoms (e.g. obesity) are expected to consult general practitioners (GPs) more frequently (possibly with a shorter interval between consultations). This referral bias may lead to higher estimated rates of conversion from PCOS to diabetes. We attempted to address this issue by using Bayesian methods such that our IPD can be complemented by some formal representation of external evidence from other

observational studies in similar settings. It was hoped that combining these data can limit the impact of bias that may exist in either our data or empirical studies. By using simulations, we were able to fully characterise the uncertainty about all of the parameters and propagate this uncertainty to the model. In effect, the Bayesian procedure produces a large number of simulations from the joint distribution of all of the parameters. Each of these can in turn be used to simulate potential futures, in terms of population dynamics as determined by the transitions across the states of the model.

The current model only controlled for age whereas obesity and ethnicity may influence the transition from PCOS to diabetes. For example, obesity worsens PCOS and accelerates the conversion to diabetes (Sam, 2007) and a higher risk of diabetes is observed for certain ethnic groups (Zhao and Qiao, 2013). However, since part of the risk of developing PCOS is obesity, it is in fact not possible to separate the effect of obesity and PCOS on the accelerated conversion rates of diabetes. Another reason for not including weight status and ethnicity in our model is that the information on these variables were recorded in less than 50% of the patients in the THIN database.

The estimate for the healthcare costs for PCOS is likely to be conservative for several reasons. Our previous study (Ding et al., 2016) suggested that the prevalence of PCOS estimated from THIN is much lower (by a factor of at least three) compared with community studies. Moreover, GPs are unlikely to make a diagnosis of PCOS after menopause, so the conversion rates from probable cases to diabetes may be underestimated. We assumed that women with PCOS aged above 45 develop diabetes during the follow-up at the same rate as those aged 40-45. This is conservative because an increasing prevalence of diabetes is observed in aging population. If we applied the same relative risk of diabetes across age

groups in the general population (Sharma et al., 2016) for our analysis, the prevalence of diabetes in the PCOS population was projected to be over 40% in 2039. Furthermore, the costs of treating other morbidities associated with PCOS were not included due to a lack of data, e.g. infertility, cardiovascular diseases, endometrial cancer and psychological disorders (Barry et al., 2011).

Interpretation

Our finding suggests low rates for conversion from probable to confirmed PCOS and high conversion rates from PCOS to diabetes. The failure of screening (to make a confirmed diagnosis of PCOS) and the rapid conversion from PCOS to diabetes result in over 25% of the women with PCOS being estimated to develop diabetes by 2039. This significantly impacts the QoL for individual patients (quality deficits of 0.04-0.1 measured by EQ-5D) and incurs a substantial amount of healthcare costs (a discounted present value of over £7 billion pounds) to the NHS, e.g. equivalent to the total annual spending on statins (National Institute for Health and Clinical Excellence). This further emphasises the need for a more efficient screening approach as earlier diagnosis would allow intervention to reduce the impact of the syndrome on women with PCOS (around 750,000 women in the UK).

In the USA, an HbA1c test is recommended for PCOS patients by a guideline (Legro et al., 2013) but we found that only 2.4% of women had this diabetes screening test within one year after their diagnosis of PCOS (only increasing slightly to 4% after three years of diagnosis). Screening with HbA1c has been found to be cost effective for other high-risk populations, as the test is inexpensive and facilitates intervention to prevent diabetes or reduce complications. This test is already incorporated in the NHS health check and the

National Diabetes Prevention Programme (National Health Service). These programmes target those aged 40-74 with BMI≥30 (or BMI≥27.5 for South Asian population) in whom the incidence of diabetes ranges from 14.3 to 23.8 per 1000 PY (Tillin et al., 2015). Our finding that the incidence is 10-30 per 1000 PY in women with PCOS aged below 45 suggests a possible role for screening PCOS patients to improve prevention and allow early diagnosis of diabetes.

Based on our results, it is possible that expanding the target population of NHS health check and the National Diabetes Prevention Programme to include women with a diagnosis of PCOS or symptoms suggestive of PCOS may be cost effective. This is because an HbA1c test is cheap compared to the cost of a delayed diagnosis of diabetes. Estimates from the USA and now the UK suggest that failure to identify this high-risk population incurs substantial healthcare spending.

Conclusion

The results of this study highlight the considerable number of women whose diagnosis of PCOS is uncertain and their potential missed opportunity for prevention or early treatment of diabetes. Consequently, women with PCOS suffer long-term reduction in quality of life and this incurs a high level of expenditure for the NHS. Based on the incidence of diabetes, expanding the current targeted populations in diabetes prevention programmes to include women with PCOS may be cost effective.

Authors' roles

T.D. contributed to the study design, analysis and interpretation of the data and drafted the article and revised it critically for important intellectual content. G.B. contributed to the analysis and interpretation of data, revised the manuscript critically for important intellectual content and gave final approval of the version to be published. P.J.H and I.P. revised the article critically for important intellectual content and gave final approval of the version to be published.

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Competing interests

None declared.

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Figure 1. Overview of the health states included in the Markov model. Rounded rectangles represent a single health state. Arrows indicate that women can move across two states (from the one at which the arrow originates, to the one where it ends). The absence of an arrow connecting two nodes encodes the assumption that a particular transition is not possible. The state of death is an absorbing state and individuals from any state can move there and then remain forever.

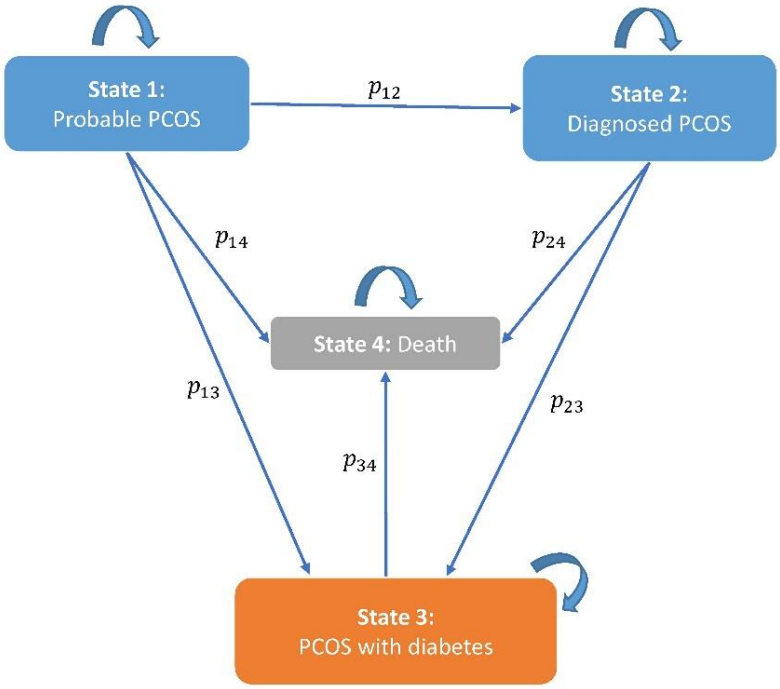
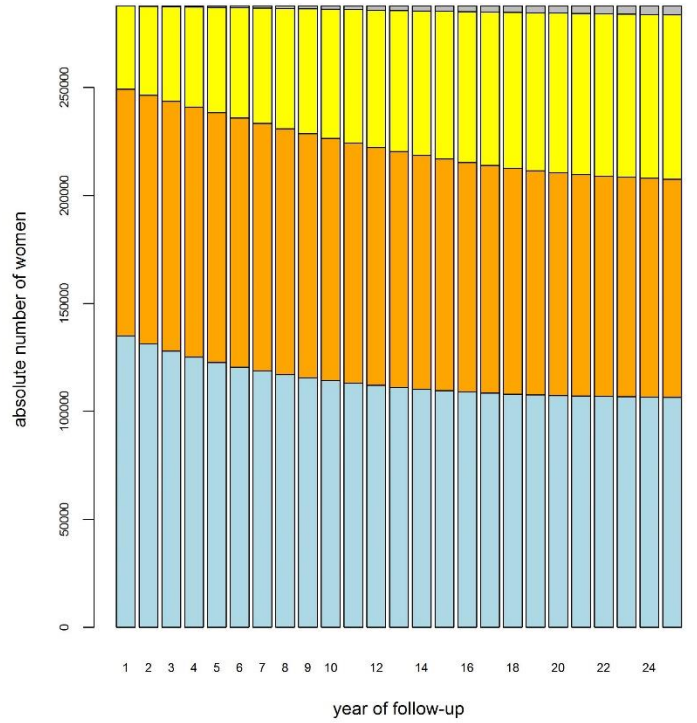


Figure 2. Distribution of patients (absolute number) over states in the follow-up period: (a) closed cohort model (top); (b) open cohort model (bottom).



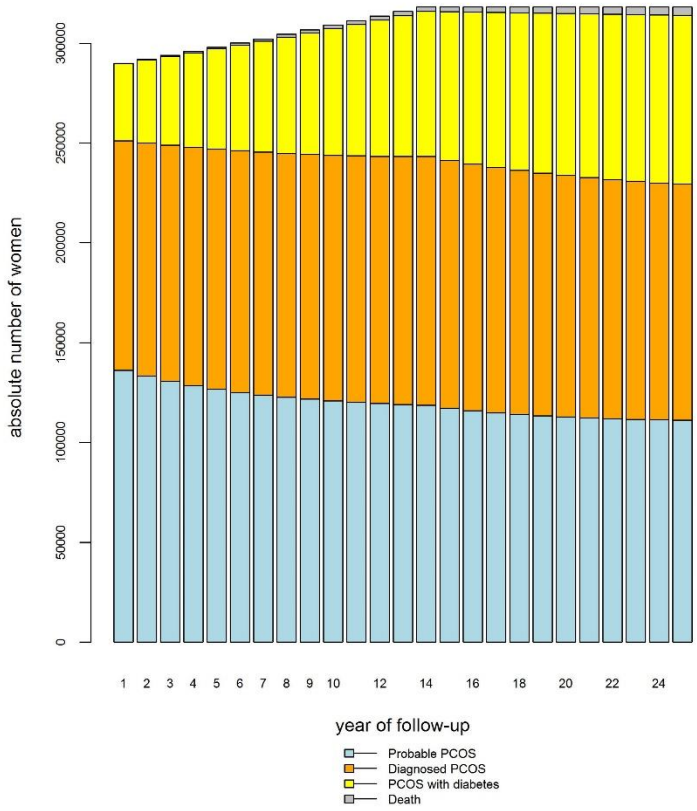


Figure 3. Economic burden of PCOS in the UK over the follow-up period (2014-2039). Results for open cohort model are shown here.

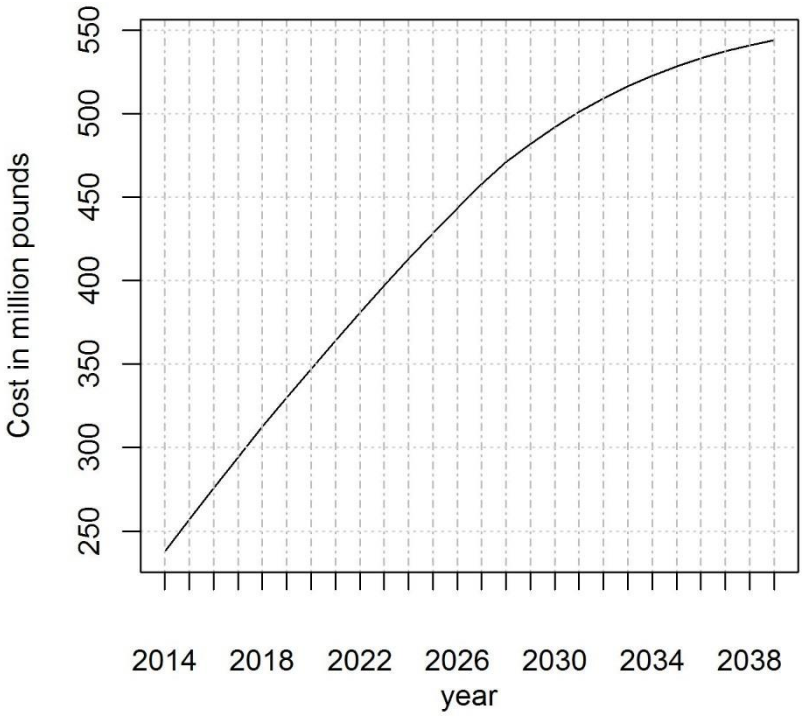


Figure 4. Quality of life measured by EQ-5D simulated for the PCOS cohort (yellow line) and a healthy cohort (blue line) in the UK over the follow-up period (2014-2039). Data points on the curve represent the quality of life for the entire cohort at a given time point. Note that the area under the curve can be considered as the Quality Adjusted Life Years (QALYs) for each cohort. The shaded area in grey represents the difference in QALYs comparing PCOS and the healthy cohort. Results for open cohort model are shown here.