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**Epidemiology of endometriosis: a large population-based database study in a 2-million-member  
health care provider**

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**Running title:** Real-world epidemiology of endometriosis in Israel

**ABSTRACT**

**Objective:** Endometriosis constitutes a significant burden on the quality of life of women, their families, and health systems. The objective of this study is to describe the real-world epidemiology of endometriosis in an unselected low-risk population in Israel.

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**Design:** Retrospective population-based study.

**Setting and population:** The computerized databases of Maccabi Healthcare Services (MHS), a 2-million-member healthcare provider representing a quarter of the Israeli population.

**Methods:** The crude point prevalence (31/12/2015; diagnosed since 1998) and annual incidence (2000-2015) rates of diagnosed endometriosis (ICD-9-CM 617.xx) were assessed among women aged 15-55 years. Prevalent patients were characterized in terms of socio-demographic and clinical characteristics, including validated MHS infertility and chronic disease registries.

**Main outcome measures:** prevalence and incidence of diagnosed endometriosis in MHS.

**Results:** The point prevalence of endometriosis (N=6146, mean age  $40.4 \pm SD 8.0$  years) was 10.8 per 1000 (95% CI 10.5-11.0). Women aged 40-44 had the highest prevalence rate of 18.6 per 1000 (95% CI 17.7-19.5). Infertility was documented in 37% of patients. A total of 6,045 patients were included in the cohort of newly-diagnosed endometriosis (mean age  $34.0 \pm 8.1$  years), corresponding to an average annual incidence rate of 7.2 per 10,000 (95% CI 6.5-8.0).

**Conclusion:** We observed a substantially lower prevalence of diagnosed endometriosis compared to previous reports in high-risk populations, in line with population-based estimates from European databases (range 0.8-1.8%). Further characterization of this cohort may help to understand what affects the prevalence of endometriosis in Israel and to promote earlier diagnosis and improve management in clinical practice.

**Funding sources:** None.

**Keywords:** Endometriosis, epidemiology, diagnosis, prevalence

**Tweetable abstract:** Endometriosis diagnosed in 1% of women, according to a large population-based study in a community setting.

## INTRODUCTION

Endometriosis refers to the presence of endometrial tissue (glands and stroma) in locations outside the uterus. It is a recurring persistent disease that may present as chronic pelvic pain, fatigue, dysmenorrhea, dyspareunia, dysuria, dyschesia and subfertility.<sup>1,2</sup> The true prevalence rates in the general population are not known mainly because diagnosis is often overlooked by primary care physicians<sup>3</sup> and delayed for an average of 10 years.<sup>4-6</sup> Endometriosis constitutes a significant burden on the quality of life of women and their families, as well as on health systems.<sup>4</sup> . Accurate assessment of endometriosis burden requires detailed information of its occurrence and prevalence.

Published prevalence estimates suggest that endometriosis affects as much as 10% of premenopausal women worldwide,<sup>1,2</sup> and approximately 30-50% of symptomatic women,<sup>7</sup> but these studies are typically limited by selection of high risk patients. The true prevalence of endometriosis in a real-world community setting is not sufficiently established.

The objective of this study is to describe the epidemiology of endometriosis in an unselected low risk population in Israel.

## METHODS

### Study design and setting

A retrospective population-based study was performed using the computerized databases of Maccabi Healthcare Services (MHS), the second largest of four recognized healthcare providers in Israel. MHS has approximately 2 million active members, in a context of universal and mandatory health insurance, such that the database represents 25% of the national population and shares similar socio-demographic characteristics.<sup>8</sup> The MHS databases include longitudinal data computerized since 1993 and integrate data from the MHS central laboratory, medication purchases, consultations with physicians, hospitalizations, procedures, and socio-demographic data linked at the level of patients' unique national identity numbers. Physician diagnoses are coded using the *International Classification of Disease, 9th Edition, clinical modification* (ICD-9-CM), and procedures are documented using *Current Procedural Terminology* (CPT) codes.

### Case ascertainment and study population selection

Endometriosis patients were identified according to diagnosis codes (ICD-9 617.xx) recorded in the MHS database. The diagnosis is a compulsory field in the electronic medical record. Cases were defined by at least one endometriosis diagnosis code from a primary care physician, gynaecologist, or other specialist during the study period 1998-2015. A total of 7,440 female MHS members met this case definition and were eligible for inclusion in the study if they met the following criteria for the prevalence and/or incidence population.

*Prevalence population:* To assess the point prevalence of diagnosed endometriosis on 31 December, 2015, all female MHS members aged 15-55 years and with at least 12 months of continuous enrolment in the health plan were included in the denominator. Among 6,801 women of all ages who met the case ascertainment criteria for prevalent endometriosis, a total of 6,146 (90.4%) were

included in the final prevalence population comprised of women aged 15-55 years. Regarding the validity of case ascertainment, 80.3% of women in this population had a diagnosis code from a gynecologist, surgeon, or hospital. Although results of imaging and surgical evaluation were not available for validation of the ICD-9 diagnosis, more than 90% of women had record of a pelvic/gynaecological ultrasound examination, with 70.5% having performed an ultrasound prior to clinical diagnosis or up to a year after diagnosis. Surgical procedures (diagnostic laparoscopy, laparoscopic adhesiolysis or laparoscopic ovarian cystectomy) were infrequently documented (5%) in this low risk population.

*Incidence population:* In order to assess the annual incidence of newly-diagnosed endometriosis during the period 2000-2015, a separate incident cohort was defined which comprised women aged 15-55 years at diagnosis who had at least 12 months of continuous enrolment prior to their first endometriosis diagnosis. For annual incidence rates, the denominator comprised all women in MHS who met these age and enrolment criteria in a given calendar year. Women aged 15-55 years accounted for 98.3% of all newly diagnosed endometriosis in 2000-2015 (N=6,149), such that the selected incidence population included 6,045 women.

#### **Study variables and definitions**

*Socio-demographic data:* Data were obtained on patients' age, residence area (North/Center/South regions), and socioeconomic status ([SES], a commercial geographic index [range: 1-10] developed by Points Ltd., which is correlated with the residence-based SES from the Israel Central Bureau of Statistics<sup>9</sup>). SES was classified into Low (1-3), Medium (4-6) and High (7-10). Body mass index (BMI) was categorized according to standard WHO cut-points.<sup>10</sup>

*Infertility:* In order to investigate the association between diagnosed infertility and endometriosis<sup>6,11</sup>, data were extracted from the MHS infertility registry, which includes all adult women who were diagnosed with subfertility or infertility, and/or underwent fertility treatments in hospital or community clinics (including in vitro fertilization, treatment with other ovarian stimulation procedures, and receipt of a donated egg), and/or purchased fertility medications.<sup>12</sup> Extensive infertility assistance is included in Israel's National Basket of Health Services,<sup>13</sup> such that financial barriers to access are limited and women with diverse characteristics are captured in MHS' infertility registry.

*Comorbidities:* To describe the clinical burden of chronic comorbidities among women with endometriosis, data were obtained from the MHS automated patient registries, which apply case ascertainment algorithms to define patients with chronic disease according to multiple data sources and disease-specific international guidelines. The MHS chronic disease registries include separate registries for cardiovascular disease (CVD),<sup>14</sup> diabetes,<sup>15</sup> hypertension,<sup>16</sup> and chronic kidney disease (CKD),<sup>17</sup> and further information may be found in previous publications. Cancer data were obtained from the Israel National Cancer Registry.<sup>18</sup> The baseline co-morbidity burden was also assessed using a modified Deyo-Charlson Comorbidity Index (CCI),<sup>19</sup> which was augmented with the MHS chronic disease registries described above in order to more accurately define chronic disease patients. Patients' smoking status was extracted from physician reports, where available, and classified into ever vs. 'never smoked.

*Healthcare resource utilization:* The number of primary care physicians and gynaecologist visits, and hospitalizations in general hospitals was measured among prevalent endometriosis patients during 2015. In addition, purchases of oral contraceptives were extracted in order to describe use among prevalent patients (i.e. at least one purchase in 2015).

## Statistical methods

Access to person-level data extracted from the MHS database was restricted to the study investigators and analyses were performed per approval of the local institutional review board. Data cleaning and management consisted primarily of recoding missing values for categorical variables (e.g. unknown SES or smoking status) and categorizing covariates as described above.

Crude age-specific rates were calculated to assess the point prevalence (31/12/2015) and average annual incidence of diagnosed endometriosis (2000-2015) per 1000 or 10,000 MHS members, respectively. Rates are displayed with 95% Fisher's confidence intervals (CI). The annual percentage change in incidence was estimated using a Poisson log-linear regression model. Descriptive statistics were generated for all analysis variables, which include frequency distributions for categorical variables (n; %) and mean values with standard deviations (SD) or median with inter-quartile range (IQR) for continuous variables. Differences between groups were tested using the  $\chi^2$  test, t-test or median test. All analyses were performed with IBM-SPSS version 22.<sup>20</sup>

## RESULTS

### Endometriosis prevalence and patient characteristics

The crude point prevalence of endometriosis was 10.8 per 1000 (95% CI 10.5-11.0). Women aged 40-44 had the highest prevalence rate of 18.6 (95% CI 17.7-19.5) per 1000 (**Fig. 1**). Prevalence rates stratified by age group, residence area, and socioeconomic status are shown in **Table 1**. The median time since diagnosis was 6.7 years (IQR 3.1-11.3). The prevalence population was characterized by a high socioeconomic status compared to the general population in MHS (**Table 1**). There was a non-significant trend towards residence in central urban areas (67%), rather than peripheral distribution.

The mean BMI was  $24.1 \pm 6.4$  kg/m<sup>2</sup>, with more than 50% of patients having a normal BMI. Infertility was documented in 36.9% of patients. The prevalence rates of selected chronic co-morbidities are described in **Table 2**. Healthcare utilization in 2015 was high, with almost all patients (94.8%) having seen a primary care physician (median 7 visits per person; IQR 3-12) and more than two thirds (68.1%) having visited a gynaecologist at least once. Oral contraceptives were purchased by 23.6% of women in the past year (and by 71.0% at any point during the study period).

### **Incidence of newly diagnosed endometriosis**

The average annual incidence rate of newly diagnosed endometriosis was 7.2 (95% CI 6.5-8.0) per 10,000 women aged 15-55 (mean age at diagnosis:  $34.0 \pm 8.1$  years). Incidence varied little throughout the 16-year period (**Fig. 2**), although there was a small but statistically significant annual percentage increase of 1.6% per (95% CI: 1.1%-2.2%;  $P < 0.001$ ). In 2015, the highest incidence rates were observed among women aged 25-39 years, particularly for the 25-29 and 35-39 age groups (**Fig. S1**).

## **DISCUSSION**

### **Main findings**

The results of this large population-based study indicate that 1.1% of women were diagnosed with endometriosis. This is similar to previous population-based estimates reporting relatively low prevalence rates in low-risk populations in a community-based setting. In the UK, the prevalence of endometriosis in the general population was estimated at 1.4-1.5%.<sup>11,21</sup> In a German population,<sup>5</sup> the highest prevalence rate was observed among women aged 35-44 years (12.8 per 1000), similar to our age-specific estimate. The average incidence rate of 72 per 100,000 in our study is



comparable to that of other published database studies in the UK,<sup>21</sup> Iceland,<sup>22</sup> and Italy,<sup>23</sup> (range 97-112 per 100,000 population), and Sweden (77 per 100,000 person-years).<sup>24</sup> Still, the true prevalence and incidence of endometriosis in real-world settings is not sufficiently established. Our results, and those of previous real-world studies cited above, are substantially lower than reports in clinical settings which estimate a prevalence of endometriosis of approximately 10%.<sup>25</sup> There is great variation in these published estimates (as much as 30-40 times),<sup>25</sup> because studies of endometriosis often select for high-risk populations, e.g. women with other gynaecological conditions, such as pelvic pain and infertility which represent a higher risk for endometriosis.

### **Strengths and limitations**

The key strength of our study is the use of a large population-based database with comprehensive longitudinal data in a low-risk setting. To date there has been a gap in real-world data on endometriosis in this country and limited evidence from population-based studies globally. Although the average income level of MHS members is slightly above the national average, this population shares similar socio-demographic characteristics and can be considered representative of the national population<sup>8</sup>. Variation in genetic and environmental factors,<sup>26</sup> as well as differences in access to health care services, should be considered when comparing results to other countries.

Our database study has several methodological limitations. Case ascertainment was entirely dependent on physician-coded diagnoses and for the purpose of this epidemiological study patients were included regardless of confirmation by surgical diagnosis. Results of imaging and surgical evaluation were not available to validate the diagnosis. However, surgical evaluation is infrequently performed in this setting. Data on potential modifiers to the ICD-9 diagnosis, such as “suspected”, “ruled out”, “assured” and “status post”, were not included as their use is inconsistent in this

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database. Nonetheless, the observation that 80% of patients were diagnosed by a specialist or in hospital, and that the majority of patients were evaluated by ultrasound, suggests a relatively high validity among patients whose follow-up primarily continues in the community without surgical evaluation. Some patients may have been diagnosed by a physician who documented endometriosis in free text in the electronic medical record, without using the diagnosis codes, and such patients were not captured in the analysis. Additionally, in the absence of a coded or written diagnosis, some patients would not have been recognized, so that the true incidence may be somewhat higher.

Other conditions such as irritable bowel syndrome (IBS), interstitial cystitis, chronic pelvic pain, and fibromyalgia may share symptoms with and could potentially be misdiagnosed as endometriosis<sup>21, 27, 28</sup>. However, given the complexity of diagnosing such conditions and the overlap that may exist between them, we would expect this to contribute to a delay in the diagnosis of endometriosis rather than a misdiagnosis. Seaman et al.<sup>27</sup> reported that women diagnosed with endometriosis were more likely than controls to be diagnosed with IBS and pelvic inflammatory disease, even after a definitive diagnosis of endometriosis, which underscores this challenge of distinguishing between misdiagnosis and co-morbidity.

Data on family history, gravity, parity, and age of menarche were not available, and these factors may be associated with the observed diagnosis of endometriosis<sup>26</sup>. Finally, analysis of symptoms and diagnostic delay was considered outside the scope of this initial epidemiological study, and merits further attention.

## Interpretation

The low prevalence estimates in our study compared to clinical studies may be explained by several reasons. First, as discussed above, endometriosis may remain undiagnosed in the general population, including among asymptomatic as well as asymptomatic women. Abbas et al. (2012) investigated predictors for endometriosis in a statutory health insurance based German cohort and found that 4.5% of all symptomatic women were diagnosed with endometriosis in a median follow-up of 4.5 years (risk ratio 4.95, 95% CI 3.67–6.68).<sup>5</sup> In a UK study, Ballard et al. estimate a risk of 4.0 to 8.1 associated with endometriosis-specific symptoms such as dysmenorrhoea, menorrhagia and ovarian cysts.<sup>21</sup> Based on physician diagnoses in the MHS database, approximately half of the women in the endometriosis prevalence population had a record of abdominopelvic pain, in line with findings from Ballard et al.<sup>21</sup>, suggesting that the MHS database may be further investigated to characterize endometriosis-related symptoms and identify predictors of endometriosis in the general population. Secondly, the true prevalence may indeed be lower than previously described in high-risk populations, as several population-based studies have suggested.<sup>11, 21, 22, 29, 30</sup>

Although annual rates of newly diagnosed endometriosis varied little throughout the 16-year period, there was a small but significant increase over time. This trend may reflect a rising incidence of endometriosis in our study population. It is also likely that increased awareness among physicians and patients contributed at least in part, to the observed trend.<sup>31</sup> Further studies will be needed to assess knowledge and attitudes to endometriosis in this health care setting.

The population was primarily comprised of women with high SES and women residing in urban central Israel, with relatively high rates of visits to a GP and gynaecologist. The annual number of GP visits per person in our study was comparable to the national average (6.2) and to the OECD average (6.6), with Israel ranked in the middle third in terms of the number of doctors per capita among OECD countries.<sup>32</sup> Socioeconomic and cultural barriers may affect access to medical care and

health-seeking behaviors. Compared to the United States, Israel's National Health Insurance law ensures more equitable access across SES, but access barriers still remain.<sup>33</sup> In the present study, over two thirds of patients visited a gynaecologist in the past year. In a previous Israeli study, immigrant women had poorer perceived health status (17% vs. 4%) and were less likely to visit a gynaecologist regularly (57% vs. 83%) and be satisfied with their primary care physician, compared to non-immigrant women.<sup>34</sup> Findings of the Women's Health in Midlife National Study in Israel among women aged 45-64 indicate that differences in utilization of primary and preventive care are primarily associated with cultural group, education, self-rated health, and health motivation, and are less likely to result from geographical or financial barriers to accessing care in the Israeli health system. In addition to cultural barriers, traditional groups such as Arab women may be less likely to visit a gynaecologist regularly due to the lack of female physicians in Israel.<sup>35</sup> Patients with low SES and/or a lower level of education may face barriers to access to specialist physicians,<sup>36, 37</sup> which could delay their diagnosis of endometriosis. In our study, there was a non-significant trend suggesting that prevalence may be higher in the central region compared to the periphery, and some geographical variation may exist within these regions, particularly with regard to access to specialist physicians and specialized ultrasound evaluations for diagnosing endometriosis.

In a context of high utilization of infertility assistance in Israel<sup>13</sup>, the age distribution of incident patients in our study, together with the high prevalence of infertility, suggest that endometriosis may often be diagnosed following fertility problems. This is consistent with previous reports on a speedier diagnosis of endometriosis when the main complaint is infertility rather than pelvic pain.<sup>6, 11</sup>

Further research may provide valuable insights into predictors of endometriosis in this database. Given the heavy burden of endometriosis on quality of life,<sup>4</sup> this study will also inform additional analyses of the economic burden of endometriosis, including direct medical costs recorded by the patients' health provider. In addition to database research, there is a need for patient-reported measurements relating to pain and other symptoms, as well as indirect costs.

## **CONCLUSION**

In conclusion, in our study we observed a prevalence of diagnosed endometriosis that is substantially lower than previous reports in high-risk populations. This supports findings from other population-based studies, providing more insight into endometriosis diagnosis in community settings. Further characterization of this cohort may help to understand the prevalence of endometriosis in symptomatic versus asymptomatic patients, to promote earlier diagnosis in clinical practice, and to better inform and increase physician awareness of the disease.

## **ACKNOWLEDGEMENTS**

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**DISCLOSURE OF INTERESTS:** None to declare. The ICMJE disclosure forms are available as online supporting information.

## **CONTRIBUTIONS TO AUTHORSHIP**

V. H. Eisenberg: study concept and design, interpretation of data, and critical revision of the manuscript for important intellectual content. C. Weil: statistical analysis and interpretation of data, and drafting of the manuscript. G. Chodick: study concept and design, interpretation of data, and critical revision of the manuscript for important intellectual content. V. Shalev: study concept and design and critical revision of the manuscript for important intellectual content.

## ETHICS APPROVAL

The study was approved by the Institutional Review Board of Assuta Medical Center in Israel (reference number 2016027 approved on 7/6/2016). Written informed consent was not required as this was a retrospective database analysis.

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#### TABLE/FIGURE CAPTION LIST

**Table 1:** Socio-demographic characteristics of prevalent endometriosis patients compared to the general population, and stratified point prevalence of diagnosed endometriosis (N=6,146; MHS 31/12/2015)

**Table 2:** Characteristics of prevalent endometriosis patients (N=6,146; MHS 31/12/2015)

**Figure 1:** Age-specific point prevalence of diagnosed endometriosis (N=6,146; MHS 31/12/2015)

**Figure 2:** Annual incidence of newly-diagnosed endometriosis (N=MHS 2010-2015). Bars, rates; line, patient counts; error bars, 95% CI.

#### ONLINE SUPPORTING INFORMATION

**Figure S1:** Age-specific annual incidence of newly-diagnosed endometriosis (MHS 2015; N=466).

Bars, rates; line, patient counts; error bars, 95% CI.

Socio-demographic characteristics		Number of women (%)		Endometriosis prevalence per 100,000 (95% CI)
		Endometriosis	Denominator	
Total		6146 (100%)	570781 (100%)	10.8 (10.5 – 11.0)
Age group, y	15 - 19	52 (0.8%)	72268 (12.7%)	0.7 (0.5 - 0.9)
	20 - 24	167 (2.7%)	64136 (11.2%)	2.6 (2.2 - 3.0)
	25 - 29	428 (7.0%)	65672 (11.5%)	6.5 (5.9 - 7.2)
	30 - 34	722 (11.7%)	65498 (11.5%)	11 (10.2 - 11.8)
	35 - 39	1187 (19.3%)	71360 (12.5%)	16.6 (15.7 - 17.6)
	40 - 44	1620 (26.4%)	87080 (15.3%)	18.6 (17.7 - 19.5)
	45 - 49	1173 (19.1%)	74246 (13%)	15.8 (14.9 - 16.7)
	50 - 55	797 (13.0%)	70521 (12.4%)	11.3 (10.5 - 12.1)
Residence area	Center	4143 (67.4%)	383302 (67.2%)	10.8 (10.5 - 11.1)
	North	1104 (18%)	101978 (17.9%)	10.8 (10.2 - 11.5)
	South	896 (14.6%)	85270 (14.9%)	10.5 (9.8 - 11.2)
	Missing	3 (0.0%)	231 (0.0%)	-
SES	Low (1-4)	833 (13.6%)	107246 (18.8%)	7.8 (7.3 - 8.3)
	Medium (5-6)	2239 (36.4%)	214156 (37.5%)	10.5 (10.0 - 10.9)
	High (7-10)	3059 (49.8%)	246903 (43.3%)	12.4 (12.0 - 12.8)
	Missing	15 (0.2%)	2476 (0.4%)	6.1 (3.5 - 9.7)

Patient characteristics		Endometriosis patients (N=6146, 100%)	
Birth region	Israel	4878	79.4%
	E. Europe	926	15.1%
	Other	292	4.8%
	Missing	50	0.8%
BMI, kg/m <sup>2</sup>	Mean ±SD	24.1 ± 6.4	
BMI category	Normal	3333	54.2%
	Underweight	481	7.8%
	Overweight	1462	23.8%
	Obese	870	14.2%
Infertility	Diagnosed and/or treated	2269	36.9%
Chronic comorbidities	Cardiovascular diseases	222	3.6%
	Hypertension	467	7.6%
	Diabetes	155	2.5%
	Cancer	240	3.9%
	Chronic kidney disease	144	2.3%
Smoking	Never smoked	5059	82.3%
	Ever smoked	933	15.2%
	Missing	154	2.5%
Healthcare resource utilization in 2015	Gynaecologist visit (≥1)	4187	68.1%
	Gynaecologist visit (≥5)	1184	19.3%
	PCP visit (≥1)	5827	94.8%
	PCP visit (≥5)	4147	67.5%
	Hospitalization (≥1)	770	12.5%

PCP, primary care physician

