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## Disease history and risk of comorbidity in the life course of a woman: a comprehensive analysis of the Japan Nurses' Health Study baseline survey

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Complete List of Authors:	Nagai, Kazue; Gunma University School of Health Sciences, Hayashi, Kunihiko; Gunma University, School of Health Sciences Yasui, Toshiyuki; Institute of Health Biosciences, The University of Tokushima Graduate School, Department of Reproductive Technology Katanoda, Kota; National Cancer Center, Iso, Hiroyasu; Osaka University Graduate School of Medicine, Public Health, Department of Social and Environmental Medicine Kiyohara, Yutaka; Kyushu University, Wakatsuki, Akihiko; Aichi Medical University School of Medicine, Department of Obstetrics and Gynecology Kubota, Toshiro; Tokyo Medical and Dental University, Department of Comprehensive Reproductive Medicine Mizunuma, Hideki; Hirosaki University School of Medicine, Department of Obstetrics and Gynecology
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Article title:

Disease history and risk of comorbidity in the life course of a woman: a comprehensive analysis of the Japan Nurses' Health Study baseline survey

Author names:

Kazue Nagai Research Fellow<sup>1</sup>, Kunihiko Hayashi Professor<sup>1</sup>, Toshiyuki Yasui Professor<sup>2</sup>, Kota Katanoda Section Head<sup>3</sup>, Hiroyasu Iso Professor<sup>4</sup>, Yutaka Kiyohara Professor<sup>5</sup>, Akihiko Wakatsuki Professor<sup>6</sup>, Toshiro Kubota Professor<sup>7</sup>, Hideki Mizunuma Professor<sup>8</sup>

Institutional affiliations:

<sup>1</sup> Unit of Community Health Sciences, Gunma University Graduate School of Health Sciences, 3-39-22 Showa-machi Maebashi, Gunma 371-8514, Japan

<sup>2</sup> Department of Reproductive Technology, Institute of Health Biosciences, The University of Tokushima Graduate School, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan

<sup>3</sup> Center for Cancer Control and Information Services, National Cancer Center, 5-1-1 Tsukiji Chuo-ku, Tokyo 104-0045, Japan

<sup>4</sup> Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka Suita, Osaka 565-0871, Japan

<sup>5</sup> Department of Environmental Medicine, Kyushu University Graduate School of Medical Sciences, 3-1-1 Maidashi Higashi-ku, Fukuoka 812-8582, Japan

<sup>6</sup> Department of Obstetrics and Gynecology, Aichi Medical University School of

1  
2  
3 Medicine, 1-1 Yazakokarimata Nagakute, Aichi 480-1195, Japan  
4

5  
6 <sup>7</sup> Department of Comprehensive Reproductive Medicine, Tokyo Medical and Dental  
7

8  
9 University, 1-5-45 Yushima Bunkyo-ku, Tokyo 113-8519, Japan  
10

11  
12 <sup>8</sup> Department of Obstetrics and Gynecology, Hirosaki University School of Medicine, 5  
13

14  
15 Zaifu-cho, Hirosaki Aomori 036-8216, Japan  
16

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32  
33 Address for correspondence and reprint requests:  
34

35  
36 Kunihiko Hayashi  
37

38  
39 Unit of Community Health Sciences, Gunma University Graduate School of Health  
40

41  
42 Sciences, 3-39-22 Showa-machi Maebashi, Gunma 371-8514, Japan  
43

44  
45 Tel: +81-27-220-8974; Fax: +81-27-220-8974  
46

47  
48 E-mail: khayashi@gunma-u.ac.jp  
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3 1 ABSTRACT

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5 2 Objective:

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8 3 To classify age at peak incidence of disease to examine the risk of comorbidities in the  
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11 4 life course of a women.

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14 5 Design:

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17 6 A cross-sectional baseline survey of the Japan Nurses' Health Study.

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20 7 Setting:

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23 8 A nationwide prospective cohort study on the health of Japanese nurses. The baseline  
24  
25 9 survey was conducted between 2001 and 2007 (n=49 927).

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28 10 Main outcome measures:

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31 11 Kaplan-Meier method and kernel smoothing technique were used to estimate age at peak  
32  
33 12 incidence of 20 diseases from a survey of Japanese women. Incidence rate and peak  
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35 13 incidence were estimated using and diseases whose peak incidence occurred before 45  
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37 14 years old or before the perimenopausal period were selected as early-onset diseases. The  
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39 15 odds ratio (OR) was estimated to examine the risk of comorbidity between early-onset  
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42 16 and other diseases.

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47 17 Results:

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50 18 The risk of comorbidity with early-onset diseases, which was significantly associated  
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52 19 with Mantel-Haenszel OR (95% confidence interval) greater than 2.00, included ovarian  
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55 20 cancer (3.65 [2.16 to 6.19]), endometrial cancer (2.40 [1.14 to 5.04]), cerebral infarction  
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21 (2.10 [1.15 to 3.85]) and a history of endometriosis; gastric cancer (3.69 [2.68 to 5.08])  
22 and a history of anaemia; transient ischemic attack (3.06 [2.29 to 4.09]), osteoporosis  
23 (2.11 ([1.71 to 2.62]), cerebral infarction (2.04 [1.26 to 3.30]), angina pectoris (2.00  
24 [1.49–2.67]) and a history of migraine; and colorectal cancer (2.31 [1.48 to 3.61]) and a  
25 history of uterine myoma. Four early-onset diseases (endometriosis, anaemia, migraine  
26 headache, and uterine myoma) were significantly correlated with one another.

27 Conclusions:

28 While there were significant associations between early-onset diseases, the women with a  
29 history of early-onset diseases had a higher risk of other diseases later in the life course.

30 Understanding the history of early-onset diseases in women may help to reduce the  
31 subsequent risk of chronic diseases in later life.

32 Key words:

33 Comorbidity, women's health, life-course approach, early-onset diseases

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35 ARTICLE SUMMARY

36 Article focus:

37 Women experience different diseases at different life stages according to reproductive  
38 health events. We attempted to classify age at peak incidence of disease and examined the  
39 risk of comorbidities.

40 Key messages:

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2  
3 41 The age at peak incidence of diseases in Japanese women varies in premenopausal,  
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5 42 perimenopausal, and postmenopausal periods.  
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8 43 The associations found in this comprehensive study between early-onset diseases (those  
9  
10 44 with a peak incidence before 45 years of age) and other diseases suggest that women with  
11  
12 45 a history of early-onset diseases have a higher risk of other diseases later in the life  
13  
14 46 course.  
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18 47 Understanding the history of early-onset diseases in women may help to reduce  
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20 48 subsequent risk of chronic diseases in later life.  
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24 49 Strengths and limitations of this study:

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27 50 Our study population, which was composed entirely of nurses, are likely to report such  
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29 51 information more accurately than the general population because of their medical  
30  
31 52 knowledge and clinical experience. We have no reason to suspect that the general  
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33 53 population of women would differ in terms of risk of comorbidity between early-onset  
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35 54 and other diseases later in the life course.  
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3 56 Introduction  
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6 57 Women experience various diseases at different life stages according to reproductive  
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8 58 health-related events such as menarche and menopause.<sup>1</sup> In particular, postmenarchal and  
9  
10 59 premenopausal women may develop oestrogen-dependent diseases such as endometriosis  
11  
12 60 and uterine myoma.<sup>2</sup> While some diseases decline in frequency after menopause, others,  
13  
14 61 such as hyperlipidaemia, occur more frequently, demonstrating that menopause represents  
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16 62 a major transition event in a woman's life course.<sup>3-5</sup>  
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22 63 In women's health, it is important to understand how the history of gynaecological  
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24 64 diseases that occur during premenopausal ages affects the risk of diseases that occur  
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26 65 during perimenopausal or postmenopausal ages, from a life-course epidemiological point  
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28 66 of view. A number of previous studies have highlighted the co-occurrence of  
29  
30 67 gynaecological diseases with other disorders, such as the increased risk of ovarian cancer  
31  
32 68 in women with endometriosis,<sup>6</sup> the association between blood oestrogen levels and  
33  
34 69 migraine in women,<sup>7,8</sup> and the link between migraine and cardiovascular risk.<sup>9</sup> However,  
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36 70 few epidemiological studies have comprehensively examined the risks of comorbidity  
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38 71 between early-onset gynaecological diseases and other subsequent chronic diseases in  
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40 72 later life.  
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50 73 The Japan Nurses' Health Study (JNHS) is a large-scale prospective cohort study  
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52 74 investigating the effects of lifestyle, healthcare practices, and history of diseases on  
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54 75 women's health.<sup>10</sup> In the cross-sectional baseline mail survey of the study, we  
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3 76 investigated the prevalence of past diagnosis and the age at first diagnosis for various  
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5 77 diseases. The study population was designed for female registered nurses, public health  
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8 78 nurses, and midwives who were at least 25 years of age and resident in Japan at the  
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11 79 baseline survey. Nurses were preferred as the study population of such an epidemiological  
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14 80 study because they were expected to report accurate medical information such as history  
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17 81 of diseases. The objectives of this study were to classify diseases that occur frequently in  
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20 82 women by identifying age at peak incidence and demonstrating their co-occurrence with  
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23 83 other diseases based on the JNHS baseline data.  
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## 28 85 Methods

### 30 86 Survey participants

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33 87 The study population comprised 49 927 female nurses who participated in the  
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36 88 cross-sectional baseline survey of the JNHS, a nationwide prospective cohort study,  
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39 89 between 2001 and 2007. The study population size was set to detect statistically an  
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42 90 increase of 1.5 or more in relative risk in the 10-years follow-up phase of the JNHS. The  
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45 91 details of the study plan and the sample size calculation have been presented elsewhere.<sup>5</sup>  
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48 92 <sup>10</sup> Data were obtained from a self-administered postal questionnaire covering a wide  
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51 93 range of health topics including lifestyle habits, disease history, reproductive health, and  
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54 94 medication use.<sup>10</sup> We included 48 632 women whose responses to the questions of disease  
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57 95 histories were completed. The JNHS study protocol was approved by the institutional  
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3 96 review boards of Gunma University and the National Institute of Public Health.  
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6 97 Participants were informed of the study's purpose and procedures before recruitment.  
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9 98 Written informed consent was provided before participation in the cohort study.  
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#### 14 100 Medical history questionnaire

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17 101 Disease history was ascertained using a questionnaire. The baseline survey investigated

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19 102 subjects' medical histories and obtained information on previous diagnoses, age at first

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21 103 diagnosis and treatment histories for a range of major medical disorders.  
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#### 26 105 Diseases analysed and definition of comorbidity

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29 106 We excluded from the analysis diseases that had a prevalence based on the diagnosis

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31 107 history of less than 0.001. We analysed 20 diseases including hypertension, angina

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33 108 pectoris, subarachnoid haemorrhage, cerebral infarction, transient ischemic attack (TIA),  
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36 109 diabetes mellitus, thyroid disease, hypercholesterolemia, cholelithiasis, endometriosis,  
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39 110 uterine myoma, cervical cancer, endometrial cancer, ovarian cancer, breast cancer, gastric  
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42 111 cancer, colorectal cancer, osteoporosis, anaemia, and migraine. Comorbidity was defined  
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45 112 as the co-occurrence of two diseases based on a subject's disease history at baseline  
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48 113 survey regardless of the timing of disease onset.  
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#### 54 115 Statistical analysis

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3 116 We estimated the cumulative incidence and 95% confidence interval (95% CI) by the  
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6 117 Kaplan-Meier survival analysis (product-limit method). In the survival analyses, we  
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9 118 treated incidence at the age of first diagnosis as an event in women with a history of the  
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11 119 disease and the observation was censored at the age recorded in the baseline survey in  
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14 120 women without a history of the disease.<sup>11</sup> We estimated the age at peak incidence using  
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16  
17 121 the kernel smoothing method (Epanechnikov kernel) and defined early-onset diseases  
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20 122 (diseases frequently occurred before the perimenopausal period) as those having a peak  
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22 123 incidence less than 45 years of age.<sup>12</sup>

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25 124 To examine the risk of comorbidity between the early-onset diseases and other diseases,  
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28 125 odds ratios (ORs) and 95% CIs were calculated. A statistical analysis was conducted to  
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31 126 examine homogeneity by the Breslow-Day test and to estimate a common odds ratio by  
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34 127 the Mantel-Haenszel method between the two age groups, comparing the age at the  
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37 128 baseline survey less than 50 years or 50 years or older. The crude ORs were also  
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40 129 calculated as a sensitive analysis. Statistical significance was set at the 5% level  
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43 130 (two-tailed) and no adjustments were made for multiplicity. All analyses were performed  
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46 131 using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

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49 133 Results

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53 134 Subject characteristics

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56 135 Of the 49 927 women who participated in the JNHS baseline survey, 48 632 who  
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3 136 responded to the questions of disease histories were included in the analysis. The average  
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6 137 age (SD) at the baseline survey was 41.2 (7.9) years. The smoking prevalence in the study  
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9 138 population was 17.2% (Table 1). In addition, 22.7% of respondents reported consuming  
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11 139 alcoholic beverages more than three times per week. Most women, 32 642 (67.1%), were  
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14 140 married at the baseline survey and 32 295 (66.4%) were parous. Only 6086 women  
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17 141 (12.5%) were postmenopausal. The average reported age at menopause (SD) in the  
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20 142 postmenopausal women was 49.1 (4.4) years.  
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#### 24 25 144 Incidence of past diagnosis by disease

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28 145 The cumulative incidences estimated by the Kaplan-Meier method at 30, 40, 50, and 60  
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31 146 years of age are shown in Table 2. The high cumulative incidence at 50 years of age,  
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34 147 around the mean age at menopause, was 29.0% for anaemia, 18.9% for uterine myoma,  
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37 148 13.0% for hypercholesterolemia, 10.7% for migraine headache, 9.0% for hypertension,  
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40 149 7.4% for endometriosis, and 6.0% for thyroid disease.

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42 150 According to the age at peak incidence of disease estimated by kernel smoothing, the  
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45 151 early-onset diseases that had a peak of incidence before 45 years of age (before the  
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48 152 perimenopausal period) were endometriosis (36.0 years), anaemia (36.0 years), migraine  
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51 153 headache (44.8 years), uterine myoma (44.8 years) and cervical cancer (44.8 years).

52  
53 154 Figure 1-a shows the kernel smoothing estimates of incidence for these early-onset  
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56 155 diseases. The peak incidence of thyroid disease, breast cancer and cholelithiasis occurred  
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3 156 between 45 and 54 years old in the perimenopausal period (Figure 1-b). For the other 12  
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6 157 diseases (subarachnoid haemorrhage, TIA, endometrial cancer, diabetes mellitus, gastric  
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9 158 cancer, cerebral infarction, ovarian cancer, colorectal cancer, angina pectoris, osteoporosis,  
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11 159 hypertension, and hypercholesterolemia), the peak incidence occurred after 55 years of  
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14 160 age or in the postmenopausal period (Table 2).  
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#### 20 162 Comorbidity among early-onset diseases

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22 163 The early-onset diseases were endometriosis, anaemia, migraine, uterine myoma and  
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24  
25 164 cervical cancer. Four early-onset diseases (endometriosis, anaemia, migraine headache,  
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28 165 and uterine myoma) were significantly correlated with one another (Table 3). It is worth  
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30  
31 166 noting that the OR (95% CI) for comorbid endometriosis and uterine myoma was 4.47  
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33 167 (4.09–4.87).  
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#### 39 169 Comorbidity of four early-onset diseases and other diseases

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42 170 The study population was stratified by age at survey into two strata, less than 50 years  
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45 171 and 50 years of age or older. Examination of ORs for homogeneity across strata using the  
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48 172 Breslow-Day test revealed that the risk of comorbidity was statistically heterogeneous for  
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51 173 hypertension and hypercholesterolemia in women with endometriosis, diabetes mellitus,  
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53 174 osteoporosis, hypertension and hypercholesterolemia in women with anaemia, thyroid  
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56 175 disease, diabetes mellitus, angina pectoris, hypertension and hypercholesterolemia in  
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3 176 women with uterine myoma (Table 3). In all of those comorbidities, the OR in the older  
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5 177 age strata was lower than in the younger age strata. The strength of the association was  
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8 178 diminished in the older strata. The only statistically negative association of anaemia and  
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11 179 diabetes mellitus was also heterogeneous between age strata (Breslow-Day test:  $P=0.028$ ),  
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14 180 indicating the negative association was stronger in older strata, with the OR changing  
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17 181 from 0.86 in  $<50$  years to 0.54 in  $\geq 50$  years of age strata.

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20 182 The Mantel-Haenszel common ORs (95% CI) greater than 2.00 for comorbid  
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22 183 endometriosis were 3.65 (2.16–6.19), 2.40 (1.14–5.04) and 2.10 (1.15–3.85) for ovarian  
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24 184 cancer, endometrial cancer and cerebral infarction, respectively. The Mantel-Haenszel  
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27 185 common OR greater than 2.00 for comorbid anaemia was 3.69 (2.68–5.08) for gastric  
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30 186 cancer. The Mantel-Haenszel common OR for comorbid anaemia and diabetes mellitus  
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33 187 was significantly lower, 0.68 (0.56–0.84). The Mantel-Haenszel common ORs greater  
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36 188 than 2.00 for comorbid migraine headache were 3.06 (2.29–4.09), 2.11 (1.71–2.62), 2.04  
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39 189 (1.26–3.30) and 2.00 (1.49–2.67) for TIA, osteoporosis, cerebral infarction and angina  
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42 190 pectoris, respectively. The Mantel-Haenszel common OR greater than 2.00 for comorbid  
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45 191 uterine myoma was 2.31 (1.48–3.61) for colorectal cancer only (Table 3).

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47 192 The crude ORs without any stratification were estimated as a sensitive analysis. The  
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50 193 similar estimates were obtained (data not shown).

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56 195 Discussion  
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3 196 The age at peak incidence of diseases in Japanese women varies in premenopausal,  
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6 197 perimenopausal, and postmenopausal periods. The early-onset diseases (those with a peak  
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8 198 incidence before 45 years of age) were endometriosis, anaemia, migraine headache,  
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11 199 uterine myoma and cervical cancer. The associations found in this comprehensive study  
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14 200 between early-onset diseases and other diseases suggest that women with a history of  
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17 201 early-onset diseases have a higher risk of other diseases later in the life course.  
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20 202 Understanding the history of early-onset diseases in women may help to reduce  
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22 203 subsequent risk of chronic diseases in later life.  
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25 204 For endometriosis, the estimated age at peak incidence was 36.0 years of age and the  
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28 205 cumulative incidence at 50 years of age was 7.4%; thus endometriosis could be  
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31 206 considered a common gynaecological disorder in relatively young women. Endometriosis  
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34 207 is characterized by excessive growth of extra-uterine endometrial tissue, resulting in  
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37 208 subsequent bleeding into the abdominal cavity and ovaries, and presenting with  
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40 209 symptoms such as peritonitis and painful defecation or urination. While levels of  
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43 210 high-sensitivity C-reactive protein (CRP), a marker of inflammation, have been found to  
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46 211 be significantly higher in women with endometriosis,<sup>13</sup> other studies have reported an  
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49 212 association between elevated blood levels of high-sensitivity CRP and ischemic stroke.<sup>14</sup>  
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52 213 <sup>15</sup> Inflammation resulting from endometriosis may therefore also be linked with an  
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55 214 increased risk of ischemic stroke. Our results suggest that endometriosis may increase the  
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58 215 risk of cerebral infarction and TIA by triggering inflammation. The Mantel-Haenszel OR  
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3 216 (95% CI) for comorbid endometriosis and ovarian cancer was 3.65 (2.16–6.19), which  
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6 217 supports the conclusions of a previous study that found that endometriosis increases the  
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9 218 risk of developing ovarian cancer.<sup>6</sup>

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11 219 Anaemia was found to have the higher cumulative incidence (29.0% at 50 years of age).

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14 220 Anaemia is highly prevalent among women and may be diagnosed following pregnancy

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17 221 or heavy menstrual bleeding caused by uterine myoma. In the present study, the peak

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20 222 incidence for anaemia occurred at 36.0 years of age. Our results imply that relatively

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22 223 young, premenopausal women are more susceptible to anaemia than older,

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25 224 postmenopausal women. Our results also suggest a strong association between anaemia

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28 225 and gastric cancer. While anaemia can occur because of gastrectomy,<sup>16</sup> pernicious

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31 226 anaemia is associated with an increased risk of gastric cancer.<sup>17–19</sup> The causal pathway,

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34 227 including a reverse effect, could not be determined because of the study's cross-sectional

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37 228 design. This study had a novel finding in that there was a significant negative association

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40 229 between anaemia and diabetes mellitus. Several studies have reported that body iron

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43 230 stores or elevated ferritin concentrations were associated with an increased risk of type 2

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46 231 diabetes mellitus,<sup>20 21</sup> potentially supporting our finding of the negative association

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49 232 between anaemia and diabetes mellitus.

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51 233 Age at incidence peak of migraine headache was 44.8 years. Several studies reported

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54 234 that migraine was associated with oestrogen levels,<sup>7 8</sup> and the incidence significantly

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57 235 increased from menarche onwards;<sup>22 23</sup> migraine also increased the risk of ischemic stroke

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3 236 and cardiovascular disease.<sup>9</sup> The present study's findings of a significantly enhanced risk  
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6 237 of TIA, cerebral infarction and angina pectoris in migraine sufferers appear to support  
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8  
9 238 this.

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11 239 The cumulative incidence at 50 years of age of uterine myoma was 18.9%. Although  
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14 240 uterine myoma is often asymptomatic, we diagnosed a number of participants with the  
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17 241 condition after undergoing cancer screening or a prenatal test. Uterine myoma is  
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20 242 associated with elevated body mass index (BMI)<sup>24</sup> and body fat percentage,<sup>25</sup> suggesting  
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23 243 that uterine myoma may be associated with obesity. Obesity is also associated with an  
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26 244 increased risk of colon cancer.<sup>26 27</sup> The Mantel-Haenszel OR of comorbid colorectal  
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29 245 cancer was 2.31 (1.48–3.61) in this study, suggesting that obesity is a potential common  
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32 246 risk factor for uterine myoma and colorectal cancer.

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34 247 The estimated age at peak incidence of not only the early-onset diseases but also other  
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37 248 diseases in this study revealed the nature of diseases in a woman's life course. The  
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40 249 diseases included hypercholesterolemia, hypertension and osteoporosis, which occur  
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43 250 more frequently among postmenopausal women over 60 years of age. The cumulative  
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46 251 incidences at 60 years of age for hypercholesterolemia, hypertension and osteoporosis  
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49 252 were 41.3%, 23.4% and 6.7%, respectively, and these diseases exhibited a marked  
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52 253 increase in incidence after the perimenopausal period.

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54 254 The peak incidence for breast cancer occurred at 50.0 years (Figure 1-b), indicating  
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57 255 that Japanese women are more likely to develop the disease before menopause rather than  
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3 256 after the perimenopausal period. Our results suggest that, unlike women in Western  
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5 257 countries where the incidence of breast cancer increases with age even after menopause,<sup>28</sup>  
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8 258 the incidence among women in Japan and other Asian settings exhibits a bell-shaped  
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11 259 pattern with a peak at 45–50 years.<sup>29</sup> Our findings therefore support the current consensus  
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14 260 that the incidence of breast cancer in Japan is higher before menopause than after.

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17 261 The present study has several limitations. Information on disease diagnosis was based  
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19 262 on self-reporting, which may have led to a misclassification of diagnoses. However,  
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22 263 nurses are likely to report such information more accurately than the general population  
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25 264 because of their medical knowledge and clinical experience. In addition, our study  
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28 265 population, which was composed entirely of nurses, was likely to exhibit different health  
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31 266 behaviours and be exposed to different risk factors compared with the general Japanese  
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34 267 population. Thus, our findings may not be generalizable to the national population,  
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37 268 reducing the present study's external validity. However, we have no reason to suspect that  
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40 269 the general population of women would differ in terms of risk of comorbidity between  
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43 270 early-onset and other diseases later in the life course. Also, data on disease histories were  
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46 271 collected retrospectively, so eligible women who had developed fatal diseases prior to the  
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49 272 survey were unable to participate. This may have led to an underestimation of disease  
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52 273 incidence. In addition, we were unable to determine the causal relationship between  
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55 274 comorbidities because of the cross-sectional design. A further analysis of the JNHS cohort  
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58 275 using follow-up data is needed to determine the causal relationships between these  
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276 comorbidities. Finally, women over the age of 60 years were underrepresented relative to  
277 other age groups in the study.

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## 279 Conclusions

280 The early-onset diseases were endometriosis, anaemia, migraine headache, uterine  
281 myoma and cervical cancer. While there were significant associations between the  
282 early-onset diseases, women with a history of early-onset diseases had a higher risk of  
283 other diseases later in the life course. Understanding the history of early-onset diseases in  
284 women may help to reduce the subsequent risk of chronic diseases in later life. Further  
285 research based on follow-up studies is needed to clarify the risk associations between  
286 these diseases.

287

## 288 Competing interest:

289 The authors report no competing interest.

## 290 Contributorship statement:

291 K Nagai analysed the data and drafted the report. K Hayashi designed and initiated the  
292 study . K Nagai, K Hayashi, T Yasui, and K Katanoda contributed to interpretation and  
293 discussion of the data and writing of the report. K Nagai, K Hayashi, T Yasui, K  
294 Katanoda, H Iso, Y Kiyohara, A Wakatsuki, T Kubota, and H Mizunuma approved the  
295 final draft to be published and agreed to account for all aspects of the work in ensuring

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3 296 that questions related to the accuracy or integrity of any part of the work are appropriately  
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6 297 investigated and resolved.  
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14 300 entry and management. We also appreciate the late Professor Dr. Toshiharu Fujita's  
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16  
17 301 contributions to the Japan Nurses' Health Study.  
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6 Figure 1-a. Kernel-smoothing estimates of incidence for early-onset diseases that the peak  
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8 occurred before 45 years old.  
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11 Figure 1-b Kernel-smoothing estimates of incidence for diseases that the peak occurred  
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13 between 45 and 54 years old.  
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Table 1. Characteristics of study population at baseline survey.

Characteristics	N	Proportion
Age (year)		
<30	938	1.9%
30-34	11 174	23.0%
35-39	10 163	20.9%
40-44	9 656	19.9%
45-49	8 155	16.8%
50-54	5 929	12.2%
55-59	2 217	4.6%
60-64	339	0.7%
65≤	61	0.1%
Smoking status		
Non-smoker	33 918	69.7%
Current smoker	8 388	17.2%
Ex-smoker	5 648	11.6%
Missing	678	1.4%
Alcohol intake		
Non-drinker	14 224	29.2%
< 3day / week	20 391	41.9%
≥ 3day / week	11 024	22.7%
Missing	2 993	6.2%
Marital status		
Unmarried	11 633	23.9%
Married	32 642	67.1%
Divorced	2 850	5.9%
Separated / Widowed	980	2.0%
Missing	527	1.1%
Pregnancy		
Never	12 786	26.3%
Ever	33 618	69.1%
Missing	2 228	4.6%
Delivery		
Never	14 328	29.5%
Ever	32 295	66.4%
Missing	2 009	4.1%
Menopause status		
Pre-menopause	40 010	82.3%
Post-menopause	6 086	12.5%
Unknown	1 947	4.0%
Missing	589	1.2%

Table 2. Incidence peak and cumulative incidence for Kaplan-Meier estimate.

	Incidence peak¶ [%]	Age at incidence peak [years]	Cumulative incidence [%]															
			30 years				40 years				50 years				60 years			
			K-M estimate	95% CI			K-M estimate	95% CI			K-M estimate	95% CI			K-M estimate	95% CI		
Endometriosis	0.25	36.0	2.19	2.07 to 2.33			4.91	4.70 to 5.12			7.36	7.06 to 7.67			7.76	7.41 to 8.12		
Anaemia	0.85	36.0	12.4	12.1 to 12.7			19.2	18.8 to 19.5			29.0	28.5 to 29.6			31.8	31.1 to 32.6		
Migraine headache	0.32	44.8	4.51	4.32 to 4.70			7.68	7.43 to 7.93			10.7	10.3 to 11.1			12.8	12.2 to 13.5		
Uterine myoma	1.11	44.8	1.22	1.12 to 1.32			6.81	6.56 to 7.07			18.9	18.3 to 19.4			22.9	22.1 to 23.7		
Cervical cancer	0.04	44.8	0.09	0.06 to 0.12			0.57	0.50 to 0.65			1.11	0.98 to 1.25			1.37	1.13 to 1.65		
Thyroid disease	0.26	49.2	1.60	1.49 to 1.71			3.41	3.24 to 3.59			6.00	5.71 to 6.31			9.39	8.64 to 10.2		
Breast cancer	0.10	50.0	0.04	0.03 to 0.06			0.33	0.27 to 0.39			1.50	1.33 to 1.70			2.72	2.20 to 3.37		
Cholelithiasis	0.23	52.2	0.44	0.38 to 0.50			1.42	1.30 to 1.54			3.26	3.03 to 3.50			6.15	5.42 to 6.96		
Subarachnoid haemorrhage	0.03	55.1	0.01	0.01 to 0.03			0.05	0.03 to 0.08			0.17	0.12 to 0.24			0.44	0.27 to 0.74		
Transient ischemic attack	0.07	55.1	0.14	0.11 to 0.18			0.29	0.24 to 0.35			0.66	0.56 to 0.77			1.50	1.10 to 2.04		
Endometrial cancer	0.02	55.9	0.00	0.00 to 0.01			0.04	0.03 to 0.07			0.16	0.11 to 0.24			0.51	0.32 to 0.81		
Diabetes mellitus	0.38	57.3	0.08	0.06 to 0.11			0.41	0.35 to 0.49			1.92	1.73 to 2.14			6.49	5.57 to 7.55		
Gastric cancer	0.05	57.3	0.03	0.02 to 0.05			0.16	0.12 to 0.21			0.52	0.42 to 0.63			0.98	0.67 to 1.43		
Cerebral infarction	0.11	58.8	0.02	0.01 to 0.03			0.06	0.04 to 0.10			0.28	0.21 to 0.37			1.36	0.95 to 1.94		
Ovarian cancer	0.06	63.9	0.06	0.04 to 0.08			0.13	0.10 to 0.17			0.28	0.21 to 0.36			0.38	0.25 to 0.57		
Colorectal cancer	0.14†	≥65*	0.01	0.00 to 0.02			0.04	0.03 to 0.07			0.34	0.26 to 0.45			0.97	0.70 to 1.34		
Angina pectoris	0.56†	≥65*	0.04	0.03 to 0.06			0.20	0.16 to 0.25			0.99	0.85 to 1.15			3.03	2.46 to 3.74		
Osteoporosis	2.23†	≥65*	0.07	0.05 to 0.09			0.26	0.21 to 0.32			1.18	1.03 to 1.35			6.73	5.73 to 7.89		
Hypertension	3.86†	≥65*	0.36	0.31 to 0.42			1.74	1.61 to 1.88			9.05	8.62 to 9.49			23.4	21.9 to 25.0		
Hypercholesterolemia	4.74†	≥65*	0.94	0.86 to 1.03			3.27	3.10 to 3.45			13.0	12.5 to 13.5			41.3	39.4 to 43.2		

\* Age at incidence peak was undetermined because age-specific incidence was hockey stick-shaped until age 65 years.

† Incidence at 65 years of age.

¶ Incidence peak was estimated by kernel-smoothing technique.

Table 3. Mantel-Haenszel common odds ratios (95% confidence interval) for comorbidities.

	Endometriosis			Anaemia			Migraine			Uterine myoma		
	MH OR	95% CI	<i>P</i> value for Breslow-Day test	MH OR	95% CI	<i>P</i> value for Breslow-Day test	MH OR	95% CI	<i>P</i> value for Breslow-Day test	MH OR	95% CI	<i>P</i> value for Breslow-Day test
Endometriosis				2.31	(2.14 - 2.50)	0.225	1.96	(1.77 to 2.17)	0.652	4.47	(4.09 to 4.87)	0.449
Anaemia	2.31	(2.14 to 2.50)	0.225				2.13	(2.01 to 2.27)	0.045	2.73	(2.57 to 2.90)	0.410
Migraine headache	1.96	(1.77 to 2.17)	0.652	2.13	(2.01 to 2.27)	0.045				1.30	(1.20 to 1.42)	0.246
Uterine myoma	4.47	(4.09 to 4.87)	0.449	2.73	(2.57 to 2.90)	0.410	1.30	(1.20 to 1.42)	0.246			
Cervical cancer	1.12	(0.74 to 1.69)	0.969	0.82	(0.64 to 1.06)	0.093	1.32	(0.98 to 1.78)	0.203	1.39	(1.04 to 1.85)	0.412
Thyroid disease	1.49	(1.27 to 1.75)	0.595	1.18	(1.07 to 1.31)	0.306	1.24	(1.09 to 1.41)	0.073	1.43	(1.27 to 1.61)	0.010
Breast cancer	1.34	(0.91 to 1.96)	0.272	0.76	(0.59 to 0.98)	0.212	0.82	(0.58 to 1.17)	0.061	1.54	(1.19 to 1.99)	0.119
Cholelithiasis	1.31	(1.04 to 1.65)	0.905	1.19	(1.04 to 1.36)	0.348	1.42	(1.20 to 1.69)	0.135	1.68	(1.44 to 1.95)	0.015
Subarachnoid haemorrhage	1.00	(0.31 to 3.22)	0.480	0.67	(0.32 to 1.38)	0.385	1.50	(0.70 to 3.21)	0.663	0.92	(0.41 to 2.05)	0.409
Transient ischemic attack	1.91	(1.26 to 2.90)	0.748	1.44	(1.09 to 1.90)	0.899	3.06	(2.29 to 4.09)	0.384	1.38	(0.99 to 1.94)	0.529
Endometrial cancer	2.40	(1.14 to 5.04)	0.632	1.20	(0.68 to 2.09)	0.110	1.97	(1.05 to 3.70)	0.634	0.78	(0.35 to 1.74)	0.678
Diabetes mellitus	1.09	(0.79 to 1.51)	0.128	0.68	(0.56 to 0.84)	0.028	0.99	(0.77 to 1.28)	0.451	1.45	(1.19 to 1.77)	<0.001
Gastric cancer	0.87	(0.43 to 1.78)	0.946	3.69	(2.68 to 5.08)	0.879	1.06	(0.65 to 1.74)	0.252	1.04	(0.66 to 1.63)	0.539
Cerebral infarction	2.10	(1.15 to 3.85)	0.447	0.89	(0.56 to 1.42)	0.987	2.04	(1.26 to 3.30)	0.581	1.39	(0.85 to 2.25)	0.120
Ovarian cancer	3.65	(2.16 to 6.19)	0.208	0.94	(0.58 to 1.53)	0.995	1.51	(0.85 to 2.66)	0.291	1.60	(0.93 to 2.76)	0.539
Colorectal cancer	1.59	(0.80 to 3.16)	0.594	1.56	(1.02 to 2.37)	0.506	1.78	(1.06 to 2.97)	0.618	2.31	(1.48 to 3.61)	0.384
Angina pectoris	1.55	(1.03 to 2.32)	0.093	1.12	(0.86 to 1.45)	0.170	2.00	(1.49 to 2.67)	0.283	1.45	(1.09 to 1.91)	<0.001
Osteoporosis	1.89	(1.43 to 2.51)	0.532	1.49	(1.24 to 1.80)	0.010	2.11	(1.71 to 2.62)	0.622	1.54	(1.24 to 1.90)	0.441
Hypertension	1.26	(1.07 to 1.47)	0.003	0.98	(0.90 to 1.08)	0.035	1.69	(1.52 to 1.90)	0.455	1.50	(1.35 to 1.66)	<0.001
Hypercholesterolemia	1.30	(1.15 to 1.47)	0.021	1.06	(0.98 to 1.14)	<0.001	1.35	(1.23 to 1.48)	0.237	1.36	(1.25 to 1.48)	<0.001

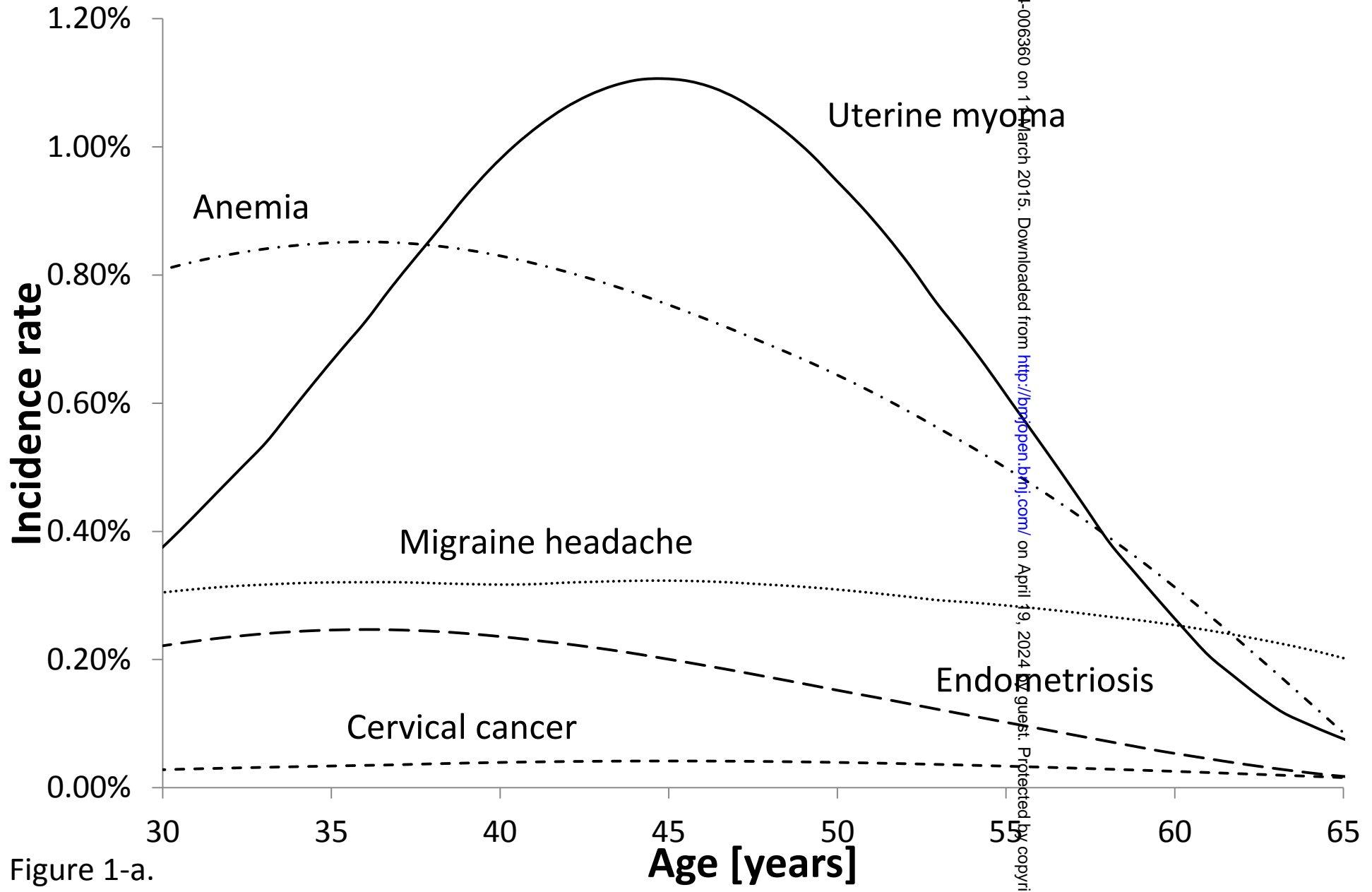


Figure 1-a.

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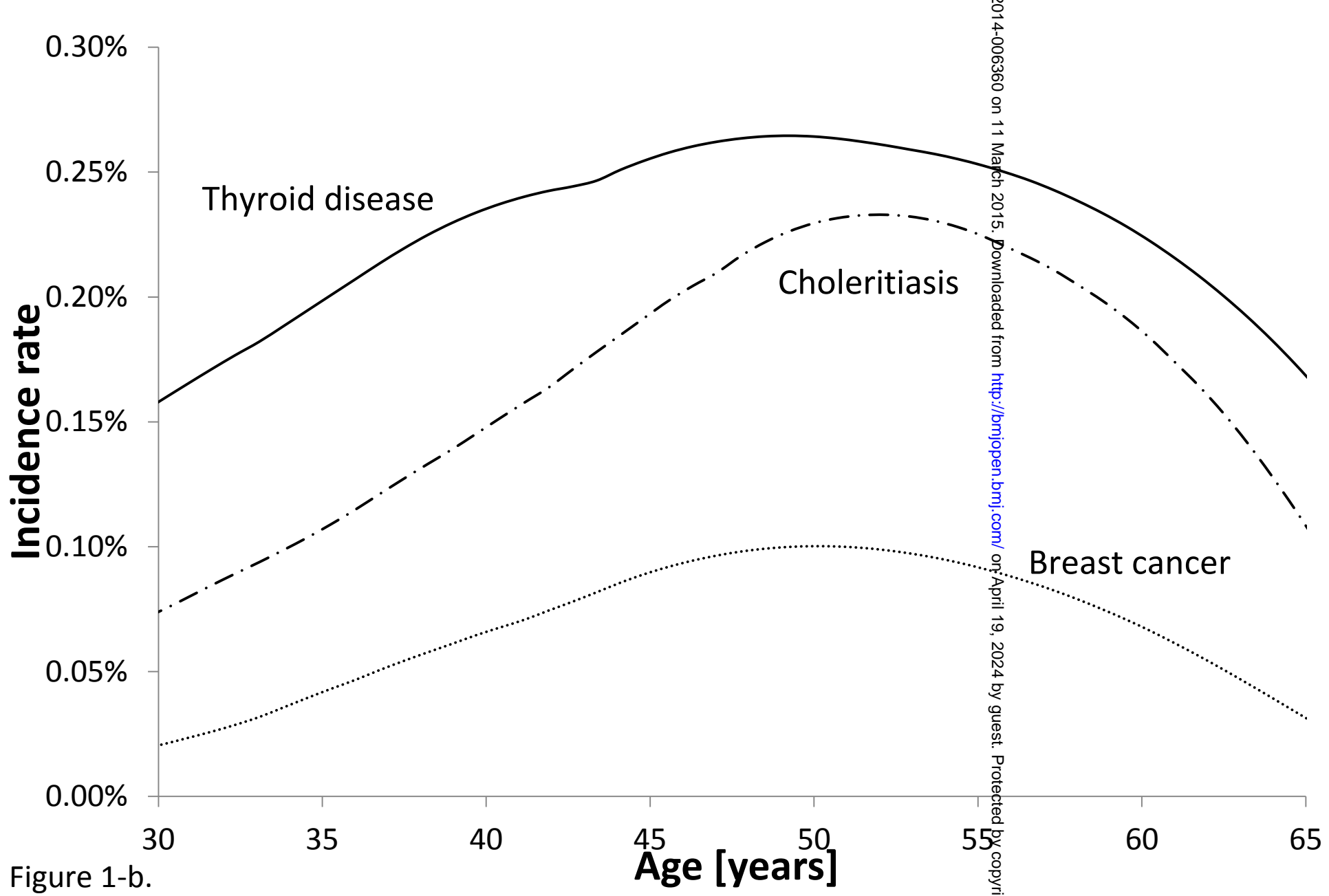


Figure 1-b.

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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
<b>Title and abstract</b>	1 <input checked="" type="checkbox"/> P.3 L.5-9	(a) Indicate the study's design with a commonly used term in the title or the abstract
	<input type="checkbox"/> P.3 L.10-P.4 L.26	(b) Provide in the abstract an informative and balanced summary of what was done and what was found
<b>Introduction</b>		
Background/rationale	2 <input checked="" type="checkbox"/> P.5 L.36-51	Explain the scientific background and rationale for the investigation being reported
Objectives	3 <input checked="" type="checkbox"/> P.5 L.60-62	State specific objectives, including any prespecified hypotheses
<b>Methods</b>		
Study design	4 <input checked="" type="checkbox"/> P.6 L.66-67	Present key elements of study design early in the paper
Setting	5 <input checked="" type="checkbox"/> P.6 L.66-74	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 <input checked="" type="checkbox"/> P.6 L.73-74	(a) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7 <input checked="" type="checkbox"/> P.7 L.80-82, 85-92	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* <input checked="" type="checkbox"/> P.7 L.80-82, 85-90	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 <input checked="" type="checkbox"/> P.6 L.58-60, P.8 L.104-107	Describe any efforts to address potential sources of bias
Study size	10 <input checked="" type="checkbox"/> P.6 L.68-70	Explain how the study size was arrived at
Quantitative variables	11 <input checked="" type="checkbox"/> P.8 L.96-102	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	<input type="checkbox"/> P.8 L.96-110	(a) Describe all statistical methods, including those used to control for confounding
	<input type="checkbox"/> P.8 L.104-108	(b) Describe any methods used to examine subgroups and interactions
	12 <input checked="" type="checkbox"/> P.6 L.73-74	(c) Explain how missing data were addressed
	<input type="checkbox"/> P.8 L.107-108	(d) If applicable, describe analytical methods taking account of sampling strategy
	<input type="checkbox"/> P.8 L.107-108	(e) Describe any sensitivity analyses
<b>Results</b>		

Participants	13*	P.8 L.114- P.9 L.115	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
	<input checked="" type="checkbox"/>	P.8 L.114- P.9 L.115	(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram
Descriptive data	14*	P.9 L.115-L.121, Table 1	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	<input checked="" type="checkbox"/>	Table 1	(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	P.9 L.124-128, Table 2	Report numbers of outcome events or summary measures
Main results	16	P.10 L.161-172, Table 3	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
	<input checked="" type="checkbox"/>	P.9 L.129-139, P.11 L.161-170	(b) Report category boundaries when continuous variables were categorized
			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	P.10 149-160	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
<input checked="" type="checkbox"/>		P.11 L.171-172	
<b>Discussion</b>			
Key results	18	P.12 L.175-180	Summarise key results with reference to study objectives
	<input checked="" type="checkbox"/>	P.14 L.226-232	
Limitations	19	P.15 L.240-256	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
<input checked="" type="checkbox"/>			
Interpretation	20	P.12 L.178-182	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
<input checked="" type="checkbox"/>		P15. L.235-239	
Generalisability	21	P.15 L.243-249	Discuss the generalisability (external validity) of the study results
<input checked="" type="checkbox"/>			
<b>Other information</b>			
Funding	22	P.16 L.274-P.17	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
	<input checked="" type="checkbox"/>	L.275	

\*Give information separately for exposed and unexposed groups.

1 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and  
2 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely  
3 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at  
4 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is  
5 available at [www.strobe-statement.org](http://www.strobe-statement.org).  
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# BMJ Open

## Disease history and risk of comorbidity in the women's life course: a comprehensive analysis of the Japan Nurses' Health Study baseline survey

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Disease history and risk of comorbidity in the women's life course: a comprehensive analysis of the Japan Nurses' Health Study baseline survey

Author names:

Kazue Nagai Research Fellow<sup>1</sup>, Kunihiro Hayashi Professor<sup>1</sup>, Toshiyuki Yasui Professor<sup>2</sup>, Kota Katanoda Section Head<sup>3</sup>, Hiroyasu Iso Professor<sup>4</sup>, Yutaka Kiyohara Professor<sup>5</sup>, Akihiko Wakatsuki Professor<sup>6</sup>, Toshiro Kubota Professor<sup>7</sup>, Hideki Mizunuma Professor<sup>8</sup>

Institutional affiliations:

<sup>1</sup> Unit of Community Health Sciences, Gunma University Graduate School of Health Sciences, 3-39-22 Showa-machi Maebashi, Gunma 371-8514, Japan

<sup>2</sup> Department of Reproductive Technology, Institute of Health Biosciences, University of Tokushima Graduate School, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan

<sup>3</sup> Center for Cancer Control and Information Services, National Cancer Center, 5-1-1 Tsukiji Chuo-ku, Tokyo 104-0045, Japan

<sup>4</sup> Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka Suita, Osaka 565-0871, Japan

<sup>5</sup> Department of Environmental Medicine, Kyushu University Graduate School of Medical Sciences, 3-1-1 Maidashi Higashi-ku, Fukuoka 812-8582, Japan

<sup>6</sup> Department of Obstetrics and Gynecology, Aichi Medical University School of Medicine, 1-1 Yazakokarimata Nagakute, Aichi 480-1195, Japan

<sup>7</sup> Department of Comprehensive Reproductive Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima Bunkyo-ku, Tokyo 113-8519, Japan

<sup>8</sup> Department of Obstetrics and Gynecology, Hirosaki University School of Medicine, 5 Zaifu-cho, Hirosaki Aomori 036-8216, Japan

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Address for correspondence and reprint requests:

Kunihiko Hayashi

Unit of Community Health Sciences, Gunma University Graduate School of Health

Sciences, 3-39-22 Showa-machi Maebashi, Gunma 371-8514, Japan

Tel: +81-27-220-8974; Fax: +81-27-220-8974

E-mail: [khayashi@gunma-u.ac.jp](mailto:khayashi@gunma-u.ac.jp)

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2  
3 1 ABSTRACT

4  
5 2 Objective:

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8 3 To classify diseases based on age at peak incidence to identify the risk factors for later  
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11 4 disease in the women's life course.

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14 5 Design:

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17 6 A cross-sectional baseline survey of participants in the Japan Nurses' Health Study.

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20 7 Setting:

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23 8 A nationwide, prospective cohort study on the health of Japanese nurses. The baseline  
24  
25 9 survey was conducted between 2001 and 2007 (n=49 927).

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28 10 Main outcome measures:

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30  
31 11 Age at peak incidence for 20 diseases from a survey of Japanese women was estimated  
32  
33 12 using the Kaplan–Meier method with the kernel smoothing technique. The incidence rate  
34  
35  
36 13 and peak incidence for diseases whose peak incidence occurred before the age of 45 years  
37  
38  
39 14 or before the perimenopausal period were selected as early-onset diseases. The odds ratio  
40  
41  
42 15 (OR) and 95% confidence interval (95% CI) were estimated to examine the risk of  
43  
44  
45 16 comorbidity between early-onset and other diseases.

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48 17 Results:

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50  
51 18 Four early-onset diseases (endometriosis, anaemia, migraine headache, and uterine  
52  
53 19 myoma) were significantly correlated with one another. Late-onset diseases significantly  
54  
55  
56 20 associated (OR >2) with early-onset diseases included comorbid endometriosis with  
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2  
3 21 ovarian cancer (3.65 [2.16–6.19]), endometrial cancer (2.40 [1.14–5.04]), and cerebral  
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5 22 infarction (2.10 [1.15–3.85]); comorbid anaemia with gastric cancer (3.69 [2.68–5.08]);  
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7  
8 23 comorbid migraine with transient ischemic attack (3.06 [2.29–4.09]), osteoporosis (2.11  
9  
10  
11 24 ([1.71–2.62]), cerebral infarction (2.04 [1.26–3.30]), and angina pectoris (2.00 [1.49–  
12  
13  
14 25 2.67]); and comorbid uterine myoma with colorectal cancer (2.31 [1.48–3.61]).  
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## 17 Conclusions:

18  
19 27 While there were significant associations between four early-onset diseases, women with  
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21  
22 28 a history of one or more of the early-onset diseases had a higher risk of other diseases  
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24  
25 29 later in life course. Understanding the history of early-onset diseases in women may help  
26  
27  
28 30 reduce the subsequent risk of chronic diseases in later life.  
29

## 31 Key words:

32 32 Comorbidity, women's health, life-course approach, early-onset diseases  
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## 39 ARTICLE SUMMARY

### 41 Article focus:

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43  
44 36 Women experience different diseases at different life stages according to reproductive  
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46  
47 37 health events. We attempted to classify the age at peak incidence of disease and examined  
48  
49  
50 38 the risk of comorbidities.  
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### 52 Key messages:

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55 40 The age at peak incidence of diseases in Japanese women varies in the premenopausal,  
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3 41 perimenopausal, and postmenopausal periods. The associations found in this  
4  
5 42 comprehensive study between early-onset diseases (those with a peak incidence before 45  
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8 43 years of age) and other diseases suggest that women with a history of early-onset diseases  
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11 44 have a higher risk of other diseases later in life course. Understanding the history of  
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13  
14 45 early-onset diseases in women may help reduce the subsequent risk of chronic diseases in  
15  
16 46 later life.

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18  
19 47 Strengths and limitations of this study:

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21  
22 48 Our study population, which was composed entirely of nurses, are likely to report such  
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24  
25 49 information more accurately than the general population because of their medical  
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27  
28 50 knowledge and clinical experience. We have no reason to suspect that the general  
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31 51 population of women would differ in terms of risk of comorbidity between early-onset  
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33 52 and other diseases later in life course.  
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3 54 Introduction  
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6 55 Women experience various diseases at different life stages that correspond with  
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8 56 reproductive health-related events such as menarche and menopause.<sup>1</sup> In particular,  
9  
10 57 postmenarchal and premenopausal women may develop oestrogen-dependent diseases  
11  
12 58 such as endometriosis and uterine myoma.<sup>2</sup> While some diseases decline in frequency  
13  
14 59 after menopause, others, such as hyperlipidaemia, occur more frequently, demonstrating  
15  
16 60 that menopause represents a major transition event in a woman's life course.<sup>3-5</sup>  
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22 61 In women's health, it is important to understand how the history of gynaecological  
23  
24 62 diseases that occur during premenopausal ages affects the risk of diseases that occur  
25  
26 63 during perimenopausal or postmenopausal ages, from a life-course epidemiological point  
27  
28 64 of view. A number of previous studies have highlighted the co-occurrence of  
29  
30 65 gynaecological diseases with other disorders, such as the increased risk of ovarian cancer  
31  
32 66 in women with endometriosis,<sup>6</sup> the association between blood oestrogen levels and  
33  
34 67 migraine in women,<sup>7,8</sup> and the link between migraine and cardiovascular risk.<sup>9</sup> However,  
35  
36 68 few epidemiological studies have comprehensively examined the risks of comorbidity  
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38 69 between early-onset gynaecological diseases and other subsequent chronic diseases in  
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40 70 later life.  
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50 71 The Japan Nurses' Health Study (JNHS) is a large-scale prospective cohort study  
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52 72 investigating the effects of lifestyle, healthcare practices, and history of diseases on  
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54 73 women's health.<sup>10</sup> In the cross-sectional baseline mail survey of the study, we  
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3 74 investigated the prevalence of past diagnosis and age at first diagnosis for various  
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5 75 diseases. The study population was designed for female registered nurses, public health  
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8 76 nurses, and midwives who were at least 25 years of age and resident in Japan at the  
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11 77 baseline survey. Nurses were preferred as the study population because they were  
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14 78 expected to accurately report medical information such as disease history. The objectives  
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17 79 of this study were to classify diseases that occur frequently in women by identifying age  
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20 80 at peak incidence and demonstrating their co-occurrence with other diseases based on the  
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22 81 JNHS baseline data.  
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## 28 83 Methods

### 30 84 Survey participants

32  
33 85 The study population comprised 49 927 female nurses who participated between 2001  
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36 86 and 2007 in the cross-sectional baseline survey of the JNHS, a nationwide prospective  
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39 87 cohort study. The size of the study population was set to detect an increase of 1.5 or more  
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42 88 in relative risk in the 10-year follow-up phase of the JNHS. The details of the study plan  
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45 89 and the sample size calculation have been presented elsewhere.<sup>5, 10</sup> Data were obtained  
46  
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48 90 from a self-administered postal questionnaire covering a range of health topics including  
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51 91 lifestyle habits, disease history, reproductive health, and medication use.<sup>10</sup> We included 48  
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54 92 632 women whose responses to the questions on disease histories were completed. The  
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57 93 JNHS study protocol was approved by the institutional review boards of Gunma  
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3 94 University and the National Institute of Public Health. Participants were informed of the  
4  
5 95 study's purpose and procedures before recruitment. Written informed consent was  
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8 96 provided before participation in the cohort study.  
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#### 11 97 12 13 98 Medical history questionnaire

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15 99 Disease history was ascertained using a questionnaire. The baseline survey investigated  
16  
17 100 subjects' medical histories and obtained information on previous diagnoses, age at first  
18  
19 101 diagnosis and treatment histories for a range of major medical disorders.  
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#### 26 27 28 103 Diseases analysed and definition of comorbidity

29  
30 104 We excluded diseases from the analysis that had a prevalence based on the diagnosis  
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32 105 history of less than 0.001. We analysed 20 diseases including hypertension, angina  
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34 106 pectoris, subarachnoid haemorrhage, cerebral infarction, transient ischemic attack (TIA),  
35  
36 107 diabetes mellitus, thyroid disease, hypercholesterolemia, cholelithiasis, endometriosis,  
37  
38 108 uterine myoma, cervical cancer, endometrial cancer, ovarian cancer, breast cancer, gastric  
39  
40 109 cancer, colorectal cancer, osteoporosis, anaemia, and migraine. Comorbidity was defined  
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42 110 as the co-occurrence of two diseases based on a subject's disease history at baseline  
43  
44 111 survey regardless of the timing of disease onset.  
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#### 53 112 54 55 113 Statistical analysis

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3 114 We estimated the cumulative incidence and 95% confidence interval (95% CI) by  
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5 115 Kaplan–Meier survival analysis (product-limit method). In the survival analyses, we  
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8 116 treated incidence at the age of first diagnosis as an event in women with a history of the  
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11 117 disease and the observation was censored at the age recorded in the baseline survey in  
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14 118 women without a history of the disease.<sup>11</sup> We estimated the age at peak incidence using  
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16  
17 119 the kernel smoothing method (Epanechnikov kernel) and defined early-onset diseases  
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20 120 (diseases occurring frequently before the perimenopausal period) as those having a peak  
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22 121 incidence at less than 45 years of age.<sup>12</sup>  
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25 122 To examine the risk of comorbidity between the early-onset diseases and other diseases,  
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27  
28 123 odds ratios (ORs) and 95% CIs were calculated. A statistical analysis was conducted to  
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30  
31 124 examine homogeneity by the Breslow–Day test and to estimate a common odds ratio by  
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34 125 the Mantel–Haenszel method between the two age groups (<50 years or ≥50 years). The  
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37 126 crude ORs were also calculated as part of a sensitivity analysis. Statistical significance  
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40 127 was set at the 5% level (two-tailed) and no adjustments were made for multiplicity. All  
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42 128 analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).  
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45 129

## 47 130 Results

### 50 131 Subject characteristics

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53 132 Of the 49 927 women who participated in the JNHS baseline survey, 48 632 who  
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56 133 responded to the questions of disease histories were included in the analysis. The average  
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3 134 age (SD) at the time of the baseline survey was 41.2 (7.9) years. The smoking prevalence  
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5 135 in the study population was 17.2% (Table 1). In addition, 22.7% of respondents reported  
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8 136 consuming alcoholic beverages more than three times per week. Most women, 32 642  
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11 137 (67.1%), were married at the time of the baseline survey and 32 295 (66.4%) were parous.  
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13  
14 138 Only 6086 women (12.5%) were postmenopausal. The average reported age at  
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16  
17 139 menopause (SD) in the postmenopausal women was 49.1 (4.4) years.  
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#### 21 22 141 Incidence of past diagnosis by disease 23

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25 142 The cumulative incidences estimated by the Kaplan–Meier method at 30, 40, 50, and  
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27  
28 143 60 years of age are shown in Table 2. The high cumulative incidence at 50 years of age,  
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31 144 around the mean age at menopause, was 29.0% for anaemia, 18.9% for uterine myoma,  
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33 145 13.0% for hypercholesterolemia, 10.7% for migraine headache, 9.0% for hypertension,  
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36 146 7.4% for endometriosis, and 6.0% for thyroid disease.  
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39 147 Based on the age at peak incidence of disease estimated by kernel smoothing, the  
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42 148 early-onset diseases that had a peak of incidence before 45 years of age (before the  
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45 149 perimenopausal period) were endometriosis (36.0 years), anaemia (36.0 years), migraine  
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48 150 headache (44.8 years), uterine myoma (44.8 years) and cervical cancer (44.8 years).

49  
50 151 Figure 1-a shows the kernel smoothing estimates of incidence for these early-onset  
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53 152 diseases. The peak incidence of thyroid disease, breast cancer and cholelithiasis occurred  
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56 153 between 45 and 54 years of age, or in the perimenopausal period (Figure 1-b). For the  
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3 154 other 12 diseases (subarachnoid haemorrhage, TIA, endometrial cancer, diabetes mellitus,  
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5 155 gastric cancer, cerebral infarction, ovarian cancer, colorectal cancer, angina pectoris,  
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8 156 osteoporosis, hypertension, and hypercholesterolemia), the peak incidence occurred after  
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11 157 55 years of age, or in the postmenopausal period (Table 2).  
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### 159 Comorbidity among early-onset diseases

160 The early-onset diseases were endometriosis, anaemia, migraine, uterine myoma and  
161 cervical cancer. Four early-onset diseases (endometriosis, anaemia, migraine headache,  
162 and uterine myoma) were significantly correlated with one another (Table 3). It is worth  
163 noting that the OR (95% CI) for comorbid endometriosis and uterine myoma was 4.47  
164 (4.09–4.87).  
165

165

### 166 Comorbidity of four early-onset diseases and other diseases

167 The study population was stratified by age at survey into two strata, less than 50 years  
168 and 50 years of age or older. Examination of ORs for homogeneity across strata using the  
169 Breslow–Day test revealed that the risk of comorbidity was statistically heterogeneous for  
170 hypertension and hypercholesterolemia in women with endometriosis, diabetes mellitus,  
171 osteoporosis, hypertension and hypercholesterolemia in women with anaemia, thyroid  
172 disease, diabetes mellitus, angina pectoris, hypertension and hypercholesterolemia in  
173 women with uterine myoma (Table 3). In all of those comorbidities, the OR in the older  
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3 174 age stratum was lower than in the younger age stratum. The strength of the association  
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5 175 was diminished in the older stratum. The only statistically negative association of  
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8 176 anaemia and diabetes mellitus was also heterogeneous between age strata (Breslow–Day  
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11 177 test:  $P=0.028$ ), indicating that the negative association was stronger in the older stratum,  
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14 178 with the OR changing from 0.86 in  $<50$  years to 0.54 in the  $\geq 50$  years of age stratum.

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16  
17 179 The common ORs (95% CI) greater than 2.00 for comorbid endometriosis were 3.65  
18  
19 180 (2.16–6.19), 2.40 (1.14–5.04) and 2.10 (1.15–3.85) for ovarian cancer, endometrial cancer  
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22 181 and cerebral infarction, respectively. The common OR greater than 2.00 for comorbid  
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24  
25 182 anaemia was 3.69 (2.68–5.08) for gastric cancer. The common OR for comorbid anaemia  
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27  
28 183 and diabetes mellitus was significantly lower, 0.68 (0.56–0.84). The common ORs greater  
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31 184 than 2.00 for comorbid migraine headache were 3.06 (2.29–4.09), 2.11 (1.71–2.62), 2.04  
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33  
34 185 (1.26–3.30) and 2.00 (1.49–2.67) for TIA, osteoporosis, cerebral infarction and angina  
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36  
37 186 pectoris, respectively. The common OR greater than 2.00 for comorbid uterine myoma  
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40 187 was 2.31 (1.48–3.61) for colorectal cancer only (Table 3). The crude ORs without  
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43 188 stratification were used in a sensitivity analysis. Similar estimates were obtained (data not  
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45  
46 189 shown).

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## 50 191 Discussion

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53 192 The age at peak incidence of diseases in Japanese women varies in the premenopausal,  
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56 193 perimenopausal, and postmenopausal periods. The early-onset diseases (those with a peak  
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3 194 incidence before 45 years of age) were endometriosis, anaemia, migraine headache,  
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5 195 uterine myoma and cervical cancer. The associations found in this comprehensive study  
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8 196 between early-onset diseases and other diseases suggest that women with a history of  
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11 197 early-onset diseases have a higher risk of other diseases later in life course.  
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14 198 Understanding the history of early-onset diseases in women may help reduce any  
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17 199 subsequent risk of chronic diseases in later life.  
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20 200 In this study, we observed a skewed age distribution because of the smaller sample size  
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22 201 of participants aged 50 years or older. We stratified the study population by age at the  
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25 202 time of the survey into two strata (<50 years and  $\geq 50$  years of age) and examined the  
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28 203 homogeneity of ORs between the age groups. In addition, we estimated the common ORs  
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31 204 between the two age groups instead of overall crude ORs to adjust for the skewed age  
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34 205 distribution. However, statistical significance in the comorbidity of very late-onset  
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37 206 diseases such as osteoporosis was unlikely because of the small sample size in the older  
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40 207 age group.

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42 208 For endometriosis, the estimated age at peak incidence was 36.0 years of age and the  
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45 209 cumulative incidence at 50 years of age was 7.4%; thus, endometriosis could be  
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48 210 considered a common gynaecological disorder in relatively young women. Endometriosis  
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51 211 is characterized by excessive growth of extra-uterine endometrial tissue, resulting in  
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54 212 subsequent bleeding into the abdominal cavity and ovaries, and presenting with  
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57 213 symptoms such as peritonitis and painful defecation or urination. While levels of  
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3 214 high-sensitivity C-reactive protein (CRP), a marker of inflammation, have been found to  
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5 215 be significantly higher in women with endometriosis,<sup>13</sup> other studies have reported an  
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8 216 association between elevated blood levels of high-sensitivity CRP and ischemic stroke.<sup>14</sup>  
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11 217 <sup>15</sup> Inflammation resulting from endometriosis may therefore also be linked with an  
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14 218 increased risk of ischemic stroke. Our results suggest that endometriosis may increase the  
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17 219 risk of cerebral infarction and TIA by triggering inflammation. The OR (95% CI) for  
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20 220 comorbid endometriosis and ovarian cancer was 3.65 (2.16–6.19), which supports the  
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22 221 conclusions of a previous study that found that endometriosis increases the risk of  
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25 222 developing ovarian cancer.<sup>6</sup>

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28 223 Anaemia was found to have the higher cumulative incidence (29.0% at 50 years of age).  
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31 224 Anaemia is highly prevalent among women and may be diagnosed following pregnancy  
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34 225 or heavy menstrual bleeding caused by uterine myoma. In the present study, the peak  
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37 226 incidence for anaemia occurred at 36.0 years of age. Our results imply that relatively  
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40 227 young, premenopausal women are more susceptible to anaemia than older,  
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43 228 postmenopausal women. Our results also suggest a strong association between anaemia  
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46 229 and gastric cancer. While anaemia can occur because of gastrectomy,<sup>16</sup> pernicious  
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49 230 anaemia is associated with an increased risk of gastric cancer.<sup>17–19</sup> The causal pathway,  
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52 231 including a reverse effect, could not be determined because of the study's cross-sectional  
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55 232 design. This study had a novel finding in that there was a significant negative association  
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58 233 between anaemia and diabetes mellitus. Several studies have reported that body iron  
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234 stores or elevated ferritin concentrations were associated with an increased risk of type 2  
235 diabetes mellitus,<sup>20 21</sup> potentially supporting our finding of the negative association  
236 between anaemia and diabetes mellitus.

237 Age at incidence peak of migraine headache was 44.8 years. Several studies reported  
238 that migraine was associated with oestrogen levels,<sup>7 8</sup> and the incidence significantly  
239 increased from menarche onwards.<sup>22 23</sup> Migraine also increased the risk of ischemic  
240 stroke and cardiovascular disease in another study.<sup>9</sup> The present study's findings of a  
241 significantly enhanced risk of TIA, cerebral infarction and angina pectoris in migraine  
242 sufferers appear to support this.

243 The cumulative incidence at 50 years of age of uterine myoma was 18.9%. Although  
244 uterine myoma is often asymptomatic, we diagnosed a number of participants with the  
245 condition after undergoing cancer screening or a prenatal test. Uterine myoma is  
246 associated with elevated body mass index (BMI)<sup>24</sup> and body fat percentage,<sup>25</sup> suggesting  
247 that uterine myoma may be associated with obesity. Obesity is also associated with an  
248 increased risk of colon cancer.<sup>26 27</sup> The OR of comorbid colorectal cancer was 2.31 (1.48–  
249 3.61) in this study, suggesting that obesity is a potential common risk factor for uterine  
250 myoma and colorectal cancer.

251 The estimated age at peak incidence of not only the early-onset diseases, but also other  
252 diseases in this study, revealed the nature of diseases in a woman's life course. The  
253 diseases included hypercholesterolemia, hypertension and osteoporosis, which occur



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3 254 more frequently among postmenopausal women over 60 years of age. The cumulative  
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5 255 incidences at 60 years of age for hypercholesterolemia, hypertension and osteoporosis  
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8 256 were 41.3%, 23.4% and 6.7%, respectively, and these diseases exhibited a marked  
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11 257 increase in incidence after the perimenopausal period.

14 258 The peak incidence for breast cancer occurred at 50.0 years (Figure 1-b), indicating  
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17 259 that Japanese women are more likely to develop the disease before menopause rather than  
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20 260 after the perimenopausal period. Our results suggest that, unlike women in Western  
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22 261 countries where the incidence of breast cancer increases with age even after menopause,<sup>28</sup>  
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25 262 the incidence among women in Japan and other Asian settings exhibits a bell-shaped  
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28 263 pattern with a peak at 45–50 years.<sup>29</sup> Our findings therefore support the current consensus  
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31 264 that the incidence of breast cancer in Japan is higher before menopause than after.

33 265 The present study has several limitations. In this study, we defined disease onset as a  
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36 266 diagnosis by a medical doctor that was reported on the self-administered questionnaire.  
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39 267 Participants could only report a diagnosis; asymptomatic or undiagnosed diseases were  
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42 268 excluded. Use of diagnoses rather than self-reported prevalence may affect correlation in  
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45 269 some diseases. Information on disease diagnosis was based on self-reporting, which may  
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48 270 have led to a misclassification of diagnoses. However, nurses are likely to report such  
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51 271 information more accurately than the general population because of their medical  
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53 272 knowledge and clinical experience. In addition, our study population, which was  
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56 273 composed entirely of nurses, was likely to exhibit different health behaviours and be  
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3 274 exposed to different risk factors compared with the general Japanese population. Thus,  
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5 275 our findings may not be generalizable to the national population, reducing the present  
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8 276 study's external validity. However, we have no reason to suspect that the general  
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11 277 population of women would differ in terms of risk of comorbidity between early-onset  
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14 278 and other diseases later in life course. Additionally, data on disease histories were  
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17 279 collected retrospectively, so only living participants were included in the survey. This  
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20 280 may have led to an underestimation of disease incidence. Furthermore, we were unable to  
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23 281 determine the causal relationship between comorbidities because of the cross-sectional  
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26 282 design. Recall bias may have caused overestimation of ORs since sick people tend to  
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29 283 report more about disease history. However, the participants were nurses we think that  
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32 284 recall bias was minimized since they have medical knowledge and are more likely to have  
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35 285 answered correctly. A further analysis of the JNHS cohort using follow-up data is needed  
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38 286 to determine the causal relationships between these comorbidities. Finally, women over  
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41 287 the age of 60 years were underrepresented relative to other age groups in the study.

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44 289 Conclusions

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47 290 While there were significant associations between the four early-onset diseases  
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50 291 (endometriosis, anaemia, migraine headache, and uterine myoma), women with a history  
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53 292 of early-onset diseases had a higher risk of other diseases later in life course.  
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56 293 Understanding the history of early-onset diseases in women may help reduce the  
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3 294 subsequent risk of chronic diseases in later life. Further research based on follow-up  
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5 295 studies is needed to clarify the cause–effect associations between these diseases.  
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28 303 Contributorship statement:

29  
30 304 K Nagai analysed the data and drafted the report. K Hayashi designed and initiated the  
31  
32 305 study. K Nagai, K Hayashi, T Yasui, and K Katanoda contributed to interpretation and  
33  
34 306 discussion of the data and writing of the report. K Nagai, K Hayashi, T Yasui, K  
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36 307 Katanoda, H Iso, Y Kiyohara, A Wakatsuki, T Kubota, and H Mizunuma approved the  
37  
38 308 final draft to be published and agreed to account for all aspects of the work in ensuring  
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40 309 that questions related to the accuracy or integrity of any part of the work are appropriately  
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42 310 investigated and resolved.  
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52 312 Competing interest:

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55 313 The authors report no competing interest.  
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6 Figure 1-a. Kernel-smoothing estimates of incidence for early-onset diseases with a peak  
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8 incidence before 45 years of age.  
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11 Figure 1-b. Kernel-smoothing estimates of incidence for diseases with a peak incidence  
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13 between 45 and 54 years of age.  
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Table 1. Characteristics of study population at baseline survey.

Characteristics	N	Proportion
Age (year)		
<30	938	1.9%
30-34	11 174	23.0%
35-39	10 163	20.9%
40-44	9 656	19.9%
45-49	8 155	16.8%
50-54	5 929	12.2%
55-59	2 217	4.6%
60-64	339	0.7%
65≤	61	0.1%
Smoking status		
Non-smoker	33 918	69.7%
Current smoker	8 388	17.2%
Ex-smoker	5 648	11.6%
Missing	678	1.4%
Alcohol intake		
Non-drinker	14 224	29.2%
< 3day / week	20 391	41.9%
≥ 3day / week	11 024	22.7%
Missing	2 993	6.2%
Marital status		
Unmarried	11 633	23.9%
Married	32 642	67.1%
Divorced	2 850	5.9%
Separated / Widowed	980	2.0%
Missing	527	1.1%
Pregnancy		
Never	12 786	26.3%
Ever	33 618	69.1%
Missing	2 228	4.6%
Delivery		
Never	14 328	29.5%
Ever	32 295	66.4%
Missing	2 009	4.1%
Menopause status		
Pre-menopause	40 010	82.3%
Post-menopause	6 086	12.5%
Unknown	1 947	4.0%
Missing	589	1.2%

Table 2. Incidence peak and cumulative incidence for Kaplan–Meier estimate.

	Incidence peak¶ [%]	Age at incidence peak [years]	Cumulative incidence [%]															
			30 years			40 years			50 years			60 years						
			K-M estimate	95% CI		K-M estimate	95% CI		K-M estimate	95% CI		K-M estimate	95% CI					
Endometriosis	0.25	36.0	2.19	2.07	–	2.33	4.91	4.70	–	5.12	7.36	7.06	–	7.67	7.76	7.41	–	8.12
Anaemia	0.85	36.0	12.4	12.1	–	12.7	19.2	18.8	–	19.5	29.0	28.5	–	29.6	31.8	31.1	–	32.6
Migraine headache	0.32	44.8	4.51	4.32	–	4.70	7.68	7.43	–	7.93	10.7	10.3	–	11.1	12.8	12.2	–	13.5
Uterine myoma	1.11	44.8	1.22	1.12	–	1.32	6.81	6.56	–	7.07	18.9	18.3	–	19.4	22.9	22.1	–	23.7
Cervical cancer	0.04	44.8	0.09	0.06	–	0.12	0.57	0.50	–	0.65	1.11	0.98	–	1.25	1.37	1.13	–	1.65
Thyroid disease	0.26	49.2	1.60	1.49	–	1.71	3.41	3.24	–	3.59	6.00	5.71	–	6.31	9.39	8.64	–	10.2
Breast cancer	0.10	50.0	0.04	0.03	–	0.06	0.33	0.27	–	0.39	1.50	1.33	–	1.70	2.72	2.20	–	3.37
Cholelithiasis	0.23	52.2	0.44	0.38	–	0.50	1.42	1.30	–	1.54	3.26	3.03	–	3.50	6.15	5.42	–	6.96
Subarachnoid haemorrhage	0.03	55.1	0.01	0.01	–	0.03	0.05	0.03	–	0.08	0.17	0.12	–	0.24	0.44	0.27	–	0.74
Transient ischemic attack	0.07	55.1	0.14	0.11	–	0.18	0.29	0.24	–	0.35	0.66	0.56	–	0.77	1.50	1.10	–	2.04
Endometrial cancer	0.02	55.9	0.00	0.00	–	0.01	0.04	0.03	–	0.07	0.16	0.11	–	0.24	0.51	0.32	–	0.81
Diabetes mellitus	0.38	57.3	0.08	0.06	–	0.11	0.41	0.35	–	0.49	1.92	1.73	–	2.14	6.49	5.57	–	7.55
Gastric cancer	0.05	57.3	0.03	0.02	–	0.05	0.16	0.12	–	0.21	0.52	0.42	–	0.63	0.98	0.67	–	1.43
Cerebral infarction	0.11	58.8	0.02	0.01	–	0.03	0.06	0.04	–	0.10	0.28	0.21	–	0.37	1.36	0.95	–	1.94
Ovarian cancer	0.06	63.9	0.06	0.04	–	0.08	0.13	0.10	–	0.17	0.28	0.21	–	0.36	0.38	0.25	–	0.57
Colorectal cancer	0.14†	≥65*	0.01	0.00	–	0.02	0.04	0.03	–	0.07	0.34	0.26	–	0.45	0.97	0.70	–	1.34
Angina pectoris	0.56†	≥65*	0.04	0.03	–	0.06	0.20	0.16	–	0.25	0.99	0.85	–	1.15	3.03	2.46	–	3.74
Osteoporosis	2.23†	≥65*	0.07	0.05	–	0.09	0.26	0.21	–	0.32	1.18	1.03	–	1.35	6.73	5.73	–	7.89
Hypertension	3.86†	≥65*	0.36	0.31	–	0.42	1.74	1.61	–	1.88	9.05	8.62	–	9.49	23.4	21.9	–	25.0
Hypercholesterolemia	4.74†	≥65*	0.94	0.86	–	1.03	3.27	3.10	–	3.45	13.0	12.5	–	13.5	41.3	39.4	–	43.2

\* Age at incidence peak was undetermined because age-specific incidence was hockey stick-shaped until age 65 years.

† Incidence at 65 years of age.

¶ Incidence peak was estimated by kernel-smoothing technique.

Table 3. Mantel–Haenszel common odds ratios (95% confidence interval) for comorbidities.

	Endometriosis			Anaemia			Migraine			Uterine myoma		
	MH OR	95% CI	<i>P</i> value for Breslow–Day test	MH OR	95% CI	<i>P</i> value for Breslow–Day test	MH OR	95% CI	<i>P</i> value for Breslow–Day test	MH OR	95% CI	<i>P</i> value for Breslow–Day test
Endometriosis				2.31	(2.14 – 2.50)	0.225	1.96	(1.77 – 2.17)	0.652	4.47	(4.09 – 4.87)	0.449
Anaemia	2.31	(2.14 – 2.50)	0.225				2.13	(2.01 – 2.27)	0.045	2.73	(2.57 – 2.90)	0.410
Migraine headache	1.96	(1.77 – 2.17)	0.652	2.13	(2.01 – 2.27)	0.045				1.30	(1.20 – 1.42)	0.246
Uterine myoma	4.47	(4.09 – 4.87)	0.449	2.73	(2.57 – 2.90)	0.410	1.30	(1.20 – 1.42)	0.246			
Cervical cancer	1.12	(0.74 – 1.69)	0.969	0.82	(0.64 – 1.06)	0.093	1.32	(0.98 – 1.78)	0.203	1.39	(1.04 – 1.85)	0.412
Thyroid disease	1.49	(1.27 – 1.75)	0.595	1.18	(1.07 – 1.31)	0.306	1.24	(1.09 – 1.41)	0.073	1.43	(1.27 – 1.61)	0.010
Breast cancer	1.34	(0.91 – 1.96)	0.272	0.76	(0.59 – 0.98)	0.212	0.82	(0.58 – 1.17)	0.061	1.54	(1.19 – 1.99)	0.119
Cholelithiasis	1.31	(1.04 – 1.65)	0.905	1.19	(1.04 – 1.36)	0.348	1.42	(1.20 – 1.69)	0.135	1.68	(1.44 – 1.95)	0.015
Subarachnoid haemorrhage	1.00	(0.31 – 3.22)	0.480	0.67	(0.32 – 1.38)	0.385	1.50	(0.70 – 3.21)	0.663	0.92	(0.41 – 2.05)	0.409
Transient ischemic attack	1.91	(1.26 – 2.90)	0.748	1.44	(1.09 – 1.90)	0.899	3.06	(2.29 – 4.09)	0.384	1.38	(0.99 – 1.94)	0.529
Endometrial cancer	2.40	(1.14 – 5.04)	0.632	1.20	(0.68 – 2.09)	0.110	1.97	(1.05 – 3.70)	0.634	0.78	(0.35 – 1.74)	0.678
Diabetes mellitus	1.09	(0.79 – 1.51)	0.128	0.68	(0.56 – 0.84)	0.028	0.99	(0.77 – 1.28)	0.451	1.45	(1.19 – 1.77)	<0.001
Gastric cancer	0.87	(0.43 – 1.78)	0.946	3.69	(2.68 – 5.08)	0.879	1.06	(0.65 – 1.74)	0.252	1.04	(0.66 – 1.63)	0.539
Cerebral infarction	2.10	(1.15 – 3.85)	0.447	0.89	(0.56 – 1.42)	0.987	2.04	(1.26 – 3.30)	0.581	1.39	(0.85 – 2.25)	0.120
Ovarian cancer	3.65	(2.16 – 6.19)	0.208	0.94	(0.58 – 1.53)	0.995	1.51	(0.85 – 2.66)	0.291	1.60	(0.93 – 2.76)	0.539
Colorectal cancer	1.59	(0.80 – 3.16)	0.594	1.56	(1.02 – 2.37)	0.506	1.78	(1.06 – 2.97)	0.618	2.31	(1.48 – 3.61)	0.384
Angina pectoris	1.55	(1.03 – 2.32)	0.093	1.12	(0.86 – 1.45)	0.170	2.00	(1.49 – 2.67)	0.283	1.45	(1.09 – 1.91)	<0.001
Osteoporosis	1.89	(1.43 – 2.51)	0.532	1.49	(1.24 – 1.80)	0.010	2.11	(1.71 – 2.62)	0.622	1.54	(1.24 – 1.90)	0.441
Hypertension	1.26	(1.07 – 1.47)	0.003	0.98	(0.90 – 1.08)	0.035	1.69	(1.52 – 1.90)	0.455	1.50	(1.35 – 1.66)	<0.001
Hypercholesterolemia	1.30	(1.15 – 1.47)	0.021	1.06	(0.98 – 1.14)	<0.001	1.35	(1.23 – 1.48)	0.237	1.36	(1.25 – 1.48)	<0.001

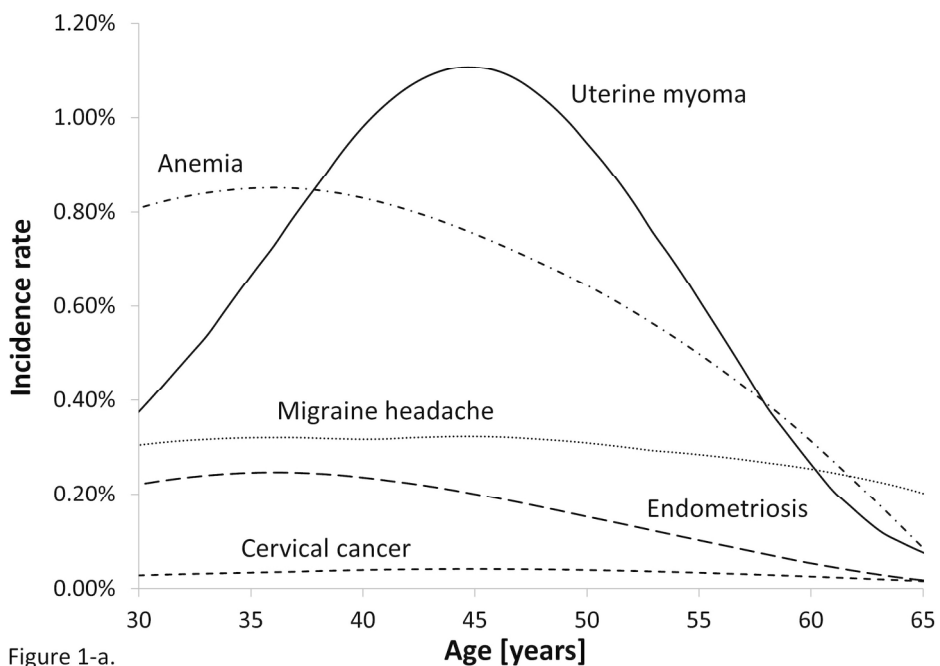


Figure 1-a.

Kernel-smoothing estimates of incidence for early-onset diseases with a peak incidence before 45 years of age.  
190x142mm (300 x 300 DPI)

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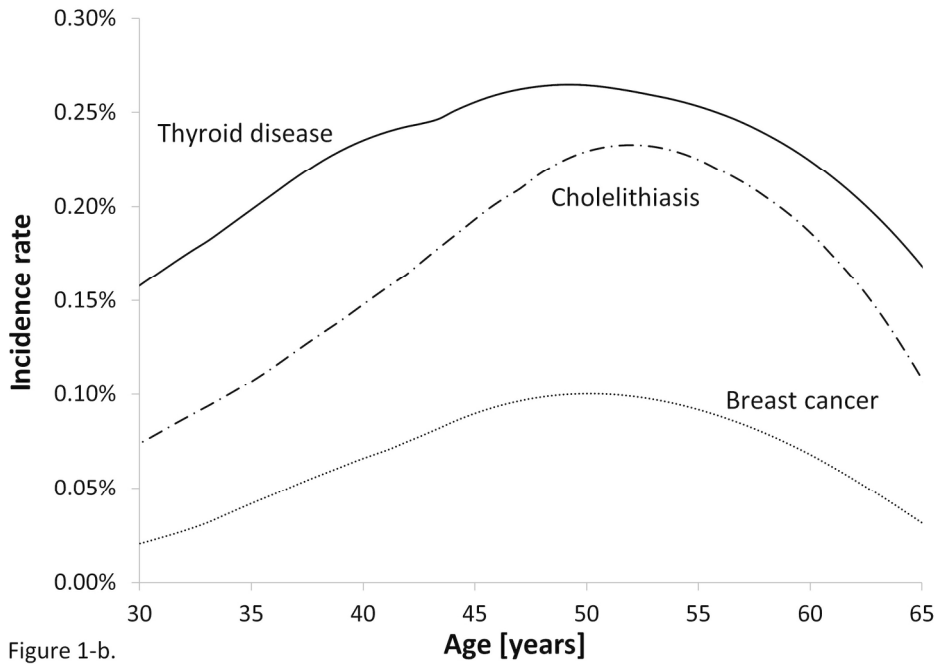


Figure 1-b.

Kernel-smoothing estimates of incidence for diseases with a peak incidence between 45 and 54 years of age.  
190x142mm (300 x 300 DPI)

Review only

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
<b>Title and abstract</b>	1 <input checked="" type="checkbox"/> P.3 L.5-9	(a) Indicate the study's design with a commonly used term in the title or the abstract
	2 <input checked="" type="checkbox"/> P.3 L.10-P.4 L.26	(b) Provide in the abstract an informative and balanced summary of what was done and what was found
<b>Introduction</b>		
Background/rationale	2 <input checked="" type="checkbox"/> P.5 L.36-51	Explain the scientific background and rationale for the investigation being reported
Objectives	3 <input checked="" type="checkbox"/> P.5 L.60-62	State specific objectives, including any prespecified hypotheses
<b>Methods</b>		
Study design	4 <input checked="" type="checkbox"/> P.6 L.66-67	Present key elements of study design early in the paper
Setting	5 <input checked="" type="checkbox"/> P.6 L.66-74	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 <input checked="" type="checkbox"/> P.6 L.73-74	(a) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7 <input checked="" type="checkbox"/> P.7 L.80-82, 85-92	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* <input checked="" type="checkbox"/> P.7 L.80-82, 85-90	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 <input checked="" type="checkbox"/> P.6 L.58-60, P.8 L.104-107	Describe any efforts to address potential sources of bias
Study size	10 <input checked="" type="checkbox"/> P.6 L.68-70	Explain how the study size was arrived at
Quantitative variables	11 <input checked="" type="checkbox"/> P.8 L.96-102	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 <input checked="" type="checkbox"/> P.8 L.96-110	(a) Describe all statistical methods, including those used to control for confounding
	12 <input checked="" type="checkbox"/> P.8 L.104-108	(b) Describe any methods used to examine subgroups and interactions
	12 <input checked="" type="checkbox"/> P.6 L.73-74	(c) Explain how missing data were addressed
	12 <input checked="" type="checkbox"/> P.6 L.73-74	(d) If applicable, describe analytical methods taking account of sampling strategy
	12 <input checked="" type="checkbox"/> P.8 L.107-108	(e) Describe any sensitivity analyses
<b>Results</b>		

1			(a) Report numbers of individuals at each stage of study—eg numbers
2		P.8 L.114- P.9	potentially eligible, examined for eligibility, confirmed eligible, included
3		L.115	in the study, completing follow-up, and analysed
4	Participants	13*	
5		<input checked="" type="checkbox"/>	P.8 L.114- P.9
6			L.115 (b) Give reasons for non-participation at each stage
7			
8			(c) Consider use of a flow diagram
9			
10			
11	Descriptive data	14*	P.9 (a) Give characteristics of study participants (eg demographic, clinical,
12			L.115-L.121, social) and information on exposures and potential confounders
13		<input checked="" type="checkbox"/>	Table 1
14			(b) Indicate number of participants with missing data for each variable of
15			interest
16			
17	Outcome data	15*	P.9 L124-128, Report numbers of outcome events or summary measures
18		<input checked="" type="checkbox"/>	Table 2
19			
20			
21	Main results	16	P.10 (a) Give unadjusted estimates and, if applicable, confounder-adjusted
22			L.161-172, estimates and their precision (eg, 95% confidence interval). Make clear
23			Table 3 which confounders were adjusted for and why they were included
24		<input checked="" type="checkbox"/>	P.9 L.129-139, (b) Report category boundaries when continuous variables were
25			P.11 L.161-170 categorized
26			
27			(c) If relevant, consider translating estimates of relative risk into absolute
28			risk for a meaningful time period
29			
30	Other analyses	17	P.10 149-160 Report other analyses done—eg analyses of subgroups and interactions,
31		<input checked="" type="checkbox"/>	P.11 L.171-172 and sensitivity analyses
32			
33			
34	<b>Discussion</b>		
35			
36	Key results	18	P.12 L.175-180 Summarise key results with reference to study objectives
37		<input checked="" type="checkbox"/>	P.14 L.226-232
38			
39	Limitations	19	Discuss limitations of the study, taking into account sources of potential
40		<input checked="" type="checkbox"/>	P.15 L.240-256 bias or imprecision. Discuss both direction and magnitude of any
41			potential bias
42			
43	Interpretation	20	P.12 L.178-182 Give a cautious overall interpretation of results considering objectives,
44		<input checked="" type="checkbox"/>	P15. L.235-239 limitations, multiplicity of analyses, results from similar studies, and
45			other relevant evidence
46			
47	Generalisability	21	P.15 L.243-249 Discuss the generalisability (external validity) of the study results
48		<input checked="" type="checkbox"/>	
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51	<b>Other information</b>		
52			
53	Funding	22	P.16 Give the source of funding and the role of the funders for the present
54		<input checked="" type="checkbox"/>	L.274-P.17 study and, if applicable, for the original study on which the present article
55			L.275 is based
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\*Give information separately for exposed and unexposed groups.



1 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and  
2 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely  
3 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at  
4 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is  
5 available at [www.strobe-statement.org](http://www.strobe-statement.org).  
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For peer review only