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Social support and ovarian cancer incidence – A Swedish prospective population-based study

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HIGHLIGHTS

- This study includes 58,000 women from a prospective Swedish cohort with 239 epithelial ovarian cancer cases.
- A validated version (SS13) of the Interview Schedule for Social Interaction (ISSI) was used.
- Quantitative (AVSI) and qualitative (AVAT) aspects of self-perceived social support were measured.
- Serous epithelial ovarian cancer was significantly associated with low scores of AVSI.
- Overall, neither AVSI nor AVAT were associated with the incidence of epithelial ovarian cancer.

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ABSTRACT

Objective. Low social support is associated with worse prognosis for epithelial ovarian cancer (EOC) patients. However, few studies have explored the relation between low social support and *incidence* of EOC. The aim of this prospective nested case-control study was to examine whether self-perceived low social support was associated with the incidence of EOC.

Methods. The Swedish Cancer Registry was used to identify participants in the Västerbotten Intervention Programme (VIP) comprising 58,000 women, who later developed EOC. Each case was matched to four cancer free controls. The VIP uses the Social Support questionnaire, a modified version of the validated questionnaire "The Interview Schedule for Social Interaction" (ISSI) measuring quantitative (AVSI) and qualitative (AVAT) aspects of social support.

Results. The risk of EOC in relation to AVSI and AVAT was similar between the 239 cases and the 941 controls after adjustment for educational level, smoking, BMI, Cambridge Physical Activity Index and age (aOR 0.85, 95% CI 0.72–1.01 and aOR 0.54, 95% CI 0.16–1.81). Lagtime was found to have no impact. A decreased risk of serous ovarian cancer was seen in women with fewer persons available for informal socializing (aOR 0.75, 95% CI 0.59–0.95). Adjusted analyses showed non-significant odds ratios below 1.0 in the vast majority of histotypes.

Conclusions. A general trend towards a decreased risk of ovarian cancer associated with low AVSI and AVAT was identified. Solely the serous subtype was significantly associated with low scores of AVSI. Prospective pathophysiological and epidemiological studies regarding social support are needed.

1. Introduction

Epithelial ovarian cancer (EOC) is the sixth most common cancer among women and has the highest mortality rate of all gynaecological cancers [1]. Even though life style factors such as overweight and smoking have shown some association with incidence of EOC, few modifiable major risk factors have been identified apart from those related to reproduction [2].

In a general population, low social support is associated with higher all-cause morbidity and mortality [3,4]. One considered reason for this association is the effect of social support on neuroendocrine regulation [5,6]. Persons with low social support show elevated levels of catecholamines in blood and urine [3–5]. Changes in activity pattern of the sympathetic nervous system, including catecholamine signalling, have been identified as one etiological factor in cancer pathogenesis [7]. Catecholamines activate β_2-adrenergic receptors and a downstream effect of this activation is an increase in radical oxygen species that causes DNA damage. Activation of β_2-adrenergic receptors also results in a downregulation of the tumor suppressor p53 [8,9]. In animal models, stress generates substantial growth of EOC cells, effectuated by norepinephrine

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and inhibited by beta-blockers [10,11]. Norepinephrine also amplifies the expression of interleukin 8 (IL-8) in EOC cells. IL-8 is a potent proangiogenic cytokine associated with tumor growth and metastasis [12]. Furthermore, the use of beta-blockers, which inhibit the effects of norepinephrine, has been associated with prolonged survival for women with EOC in some studies [13], but not all [14].

Factors measuring particularly social isolation and depression have been found to be associated with elevated levels of norepinephrine in tumor cells among patients with EOC [15,16]. Multiple studies have shown that stress hormones could enhance EOC tumour growth [10–12] and that social isolation is associated with worse survival outcomes for patients with EOC [17]. Furthermore, high levels of anxiety and depression has been associated with the expression of β_2-adrenergic receptors in tumor tissue [18]. In addition, low social support among EOC patients is associated with elevated levels of vascular endothelial growth factor [19,20], matrix metalloproteinase 9 [20], interleukin 6 [21] and down regulated activity of natural killer cells [22]. These changes promote the tumor cells' ability to form adhesions, penetrate extracellular matrix, form new blood vessels, proliferate and metastasize [7,12,19–22]. Furthermore, high social support is associated with prolonged survival compared to those with low social support among patients with EOC [17].

In general, psychological stress and depression is suggested to impair the immune response and increase the risk for cancer initiation [23]. Concerning developing EOC, a modestly increased risk has been found to be associated with depression measured 2–4 years before EOC showing decreased risk-estimates following longer lagtime [24]. On the contrary, work-characteristics in another study were not associated with increased risk of EOC [25]. Few other studies have, however, explored the relation between psychosocial factors and the *incidence* of EOC. Based on the above-mentioned circumstances, the aim of this prospective nested case-control study was to examine whether the incidence of EOC differed between women with self-perceived low social support compared to those with self-perceived high social support.

2. Materials and methods

2.1. Cohort

Umeå University Institutional Review Board approved (Dnr 2011-362-31M) this case-control study nested within the population-based Västerbotten Intervention Programme (VIP) including 58,000 women [26,27]. The Swedish Cancer Registry was used to identify cases based on the diagnosis code from the tenth revision of the International Classification of Disease (ICD-10). Cases with EOC, fallopian tube cancer (FTC) and primary peritoneal cancer (PPC) were selected. FTC and PPC share risk factor profiles, clinical and prognostic factors as well as molecular patterns with EOC, and are therefore traditionally approached as EOC in clinical and research settings [28–30]. However, PPC has in another study been found to have a separate behaviour from EOC and FTC [31]. Both cases with invasive cancer and borderline tumors with low malignant potential were included.

In the present study, cases were selected if they, prior to diagnosis, participated in the VIP. The VIP is a community intervention programme with the primary goal to reduce cardiovascular and metabolic morbidity and mortality, integrated in primary health care routine in Västerbotten County in the northern part of Sweden [26,27]. All persons at ages 40, 50 and 60 years are invited to do a clinical examination and to participate in screening for risk factors by completing a questionnaire on health and lifestyle habits [26]. Questions concerning education, employment, physical activity (the validated Cambridge index for physical activity [32]), smoking, marital status and social support were used in the present study, as well as the measurements of weight, height and blood pressure. Criteria for inclusion were: 1) a minimum of one year between participation in the VIP and cancer diagnosis, 2) no previous cancer, including in-situ cancer, except non-melanoma skin cancer and 3) that the participants had at least one ovary left. Each case was matched to four cancer-free controls from the VIP cohort regarding age (±1 year) and date of completing the questionnaire (±1 month). Participation in the VIP took place between 1985 and 2013 and the year of EOC diagnosis ranged from 1988 to 2015. The VIP does not include data regarding all known risk factors such as hereditary risk of EOC, parity, ever use of oral contraceptive pills or hormone replacement therapy. Thus, analyses regarding those risk factors were unfortunately not possible.

2.2. Assessment of social support

In the VIP, the questionnaire on risk factors contains a modified version of the validated questionnaire Social Support (SS13) [33]. SS13 is an abbreviated version of the Interview Schedule for Social Interaction (ISSI), developed to survey different perspectives on social support in population studies [33,34]. SS13 contains questions that measure the availability of social integration (AVSI) and questions that measure the availability of attachment (AVAT) [33]. The VIP does not contain all questions from SS13 and some new questions are added. The new questions were excluded since they are not part of the validated original. Therefore, in the present study, four questions regarding the *quantity* of social support (AVSI) and six questions reflecting the *quality* of social support (AVAT) were used (Table 1).

In this study, each case was required to have at least one individually matched control during the analyses, otherwise it was excluded. Since the aim of the study was to explore the potential association between social support and EOC incidence, adequate data on social support was required to be included in the study. Individuals with >1 missing answer on AVSI and those with >2 missing answers on AVAT ($n = 14$) were excluded from analyses regarding AVSI and AVAT, respectively. To compensate for missing data for those with 1 missing answer on AVSI or 1–2 missing answers on AVAT, the mean value was calculated for each individual for AVSI and AVAT respectively.

2.3. EOC diagnosis

Data on histopathology, tumour grade and behavior (borderline or invasive cancer) was retrived from the Department of Biobank research at Umeå University and from the Regional Cancer Centre North, Umeå

Table 1
The modified version of the social support questionnaire SS13.

Availability of Social Integration (AVSI)[a]
1. How many people, with the same interests as you, do you know and have contact with?
2. How many people that you know do you meet or talk to during a normal week?
3. How many friends do you have who can come to your home at any time and feel like home? They would not care if it was unclean or if you were eating. Do not count relatives.
4. How many are there with whom you can speak openly without thinking twice?
Availability of Attachment (AVAT)
1. Is there someone special from whom you really can feel support?[b]
2. Is there someone special who feels close to you?[c]
3. Do you have someone with whom you can share your innermost feelings when you feel happy? Someone whom you feel sure will feel happy simply because you are?[b]
4. Do you have someone with whom you can share your innermost feelings and really confide in?[b]
5. Does anyone ever hold or embrace you to give comfort and support?[b]
6. Do you think people, those at home or others, really appreciate what you do for them?[d]

[a] Classification of answers: None (0 points), 1–2 people (1 point), 3–5 people (2 points), 6–10 people (3 points), 11–14 people (4 points) and > 15 (5 points).
[b] Classification of answers: No (0 points), Yes (1 point).
[c] Classification of answers: No (0 points), Yes (1 point), Not sure (1 point).
[d] Classification of answers: No (0 points), Yes (1 point), Not enough (0 points).

University Hospital. A pathology report review was performed which revealed some missclassified cases that were excluded (6 metastases from other cancer sites, 8 stromal tumors and 3 germ cell tumors). Cases were grouped in type I and type II cancer [35]. Type I cancer comprised grade 1 serous, grade 1 and 2 endometrioid and all invasive mucinous tumors, while type II cancer comprised grade 2 and 3 serous, grade 3 endometrioid and undifferentiated tumors. Cases with FTC and PPC were treated like EOC during all analyses.

2.4. Statistical methods

Data was analysed using IBM SPSS Statistics 23.0. For comparison of baseline socio-demographic variables and known risk factors, Pearson's chi-square test was used for binary variables, Independent samples *t*-test for continuous variables and Mann-Whitney *U* test was used as nonparametric test for ordinal variables. Conditional logistic regression was performed in order to analyse the risk of ovarian cancer with respect to primarily social support, as well as possible confounding or mediating factors (criteria used were association with the exposure with $P < 0.1$, or changed the OR for the outcome in regression analyses > 10%). Lagtime between questionnaire and diagnosis was analysed as a linear factor as well as in stratified analyses (<5 years, >5 years). Using conditional logistic regression allowed for control of dependencies between cases and controls. All tests were two-sided and a *p*-value of 0.05 or less was considered statistically significant.

3. Results

3.1. Cases and controls

From the Swedish Cancer Registry, 270 participants in the VIP who later developed EOC, FTC or PPC were identified. In the final analyses, after exclusion of misclassified cases, 239 cases and 941 controls remained, generating a mean of 3.9 controls per case. Controls were available for all cases. Lagtime between participation in the VIP and ovarian cancer diagnosis ranged from 1 to 23 years (mean 6.8 years, median 6 years, interquartile range 3–10 years). Of the cases, 225 were diagnosed with EOC, ten with FTC and four with PPC. The distribution of histopathological subgroups was as follows: serous ($n = 129$), endometrioid ($n = 25$), mucinous ($n = 41$), clear cell carcinoma ($n = 13$), undifferentiated tumors ($n = 4$) and mixed/other ($n = 27$). Type I cancer comprised 38 of the cases while 89 were type II cancer. Invasive tumors not classified as Type I or Type II were lacking information on grade ($n = 16$), were clear cell carcinomas ($n = 13$) or had mixed histopathology ($n = 15$). Furthermore, 171 were considered invasive and 68 were of borderline malignancy. Demographic characteristics of the cases and controls are shown in Table 2.

Table 2
Demographic characteristics among cases ($n = 239$) and controls ($n = 941$). Continuous variables are presented with mean ± 1 standard deviation.

Characteristics	Case (n = 239)[a]	Control (n = 941)[a]	*P*-value
Age at survey[b] (yrs)	51.7 ± 8.4	51.7 ± 8.4	0.91
Age at diagnosis (yrs)	58.5 ± 9.5		
BMI (kg/m^2)	26.8 ± 5.4	25.9 ± 4.5	0.03
Smoking status			0.01
Smoker/ex-smoker	110 (46.4%)	336 (36.1%)	
Occasional smoker[c]	24 (10.1%)	125 (13.4%)	
Non-smoker	103 (43.5%)	469 (50.5%)	
Cambridge physical activity index			0.06
Sedentary/moderately inactive	135 (58.2%)	468 (51.3%)	
Moderately active/active	97 (41.8%)	444 (48.7%)	
Educational level			0.04
≤Nine-year primary school	77 (32.8%)	246 (26.5%)	
Secondary school[d]	108 (46.0%)	416 (44.9%)	
Higher education	50 (21.2%)	256 (28.6%)	
Employment status			0.62
Employed[e]/student	166 (81.4%)	675 (82.8%)	
Unemployed/disability pension	38 (18.6%)	140 (17.2%)	
Marital status			0.26
Married/cohabiting	58 (24.3%)	197 (20.9%)	
Unmarried/divorced/widowed	181 (75.7%)	744 (79.1%)	

[a] Numbers not identical with the total for some variables due to missing values.
[b] Matching criteria.
[c] Smokes occasionally/formerly smoked occasionally.
[d] 10–12 years of formal education.
[e] Permanent employment, temporary employment, self-employed, working at home.

3.2. Social support

No significant differences in AVSI or AVAT scores between cases and controls could be found when all histotypes were included. The mean number of persons available for informal socializing (AVSI) was 6–10 in both groups (Fig. 1A). The AVAT was highly skewed, most respondents reported full availability of intimate relationships on all the surveyed aspects. Cases and controls displayed the same pattern regarding AVAT (Fig. 1B). For detailed description of questions, see Table 1.

3.2.1. AVSI

The distribution of AVSI were similar between cases and controls, even though there was a trend towards a decreased risk of EOC associated with low AVSI in adjusted analyses (Table 3) (OR 0.93, 95% CI 0.80–1.09; aOR 0.85, 95% CI 0.72–1.01). Adjustment for potential confounding or mediating factors (educational level, smoking, BMI, Cambridge Physical Activity Index, age) showed a significantly decreased risk of serous ovarian cancer in women with a lower number of persons available for informal socializing (OR 0.87, 95% CI 0.71–1.06; aOR 0.75, 95% CI 0.59–0.95). Adjusted analyses of all other histopathological subgroups showed non-significant odds ratios below 1.0, except for the endometrioid subgroup (aOR and 95% confidence intervals for different subtypes: mucinous (0.91, 0.58–1.43); endometrioid (1.16, 0.65–2.06); type I (0.75, 0.49–1.16); type II (0.90, 0.68–1.19); borderline ovarian tumors (0.74, 0.51–1.07); invasive ovarian tumors (0.89, 0.73–1.09). Lagtime between questionnaire and diagnosis had no impact on the odds ratios, and no effect modification was found.

3.2.2. AVAT

Concerning AVAT, there was no significant difference in risk of EOC between those with low AVAT compared to those with high AVAT (Table 3) (OR 0.78, 95% CI 0.26–2.30; aOR 0.54, 95% CI 0.16–1.81). In line with AVSI, adjustment for potential confounding or mediating factors (educational level, smoking, BMI, Cambridge Physical Activity Index, age) was performed. Most histopathological subgroups showed an odds ratio below 1.0 associated with low AVAT-score (aOR and 95% confidence intervals for different subtypes: serous (0.54, 0.16–1.81); mucinous (1.42, 0.10–20.51); endometrioid (0.61, 0.04–9.24); type I (0.62, 0.05–8.19); type II (0.23, 0.02–2.59); borderline ovarian tumors (1.24, 0.14–11.33); invasive ovarian tumors (0.40, 0.09–1.83)). Lagtime between questionnaire and diagnosis did not affect the estimates.

4. Discussion

This nested case-control study within the prospective population based VIP cohort sought to determine whether the incidence of EOC differed between women with self-perceived low social support compared to those with self-perceived high social support. Altogether, no significant differences in the risk of EOC among the studied group of women were found in relation to social support, regardless measuring qualitative and/or quantitative aspects. However, the fact that the vast majority of the adjusted odds ratios were below 1.0 may reflect a possible trend towards decreased risk of EOC associated with low social support. Furthermore, in the specific subgroup of serous ovarian cancer, low AVSI

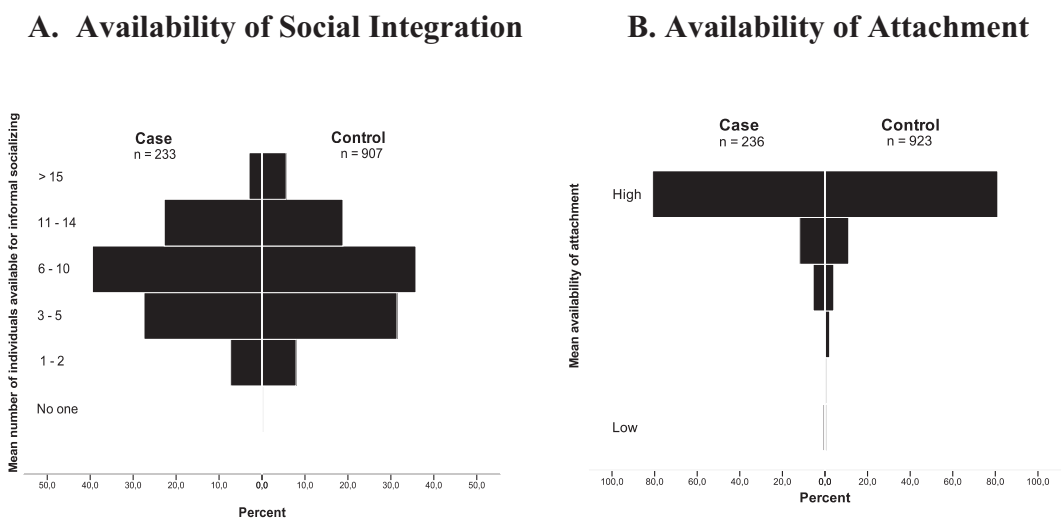

Fig. 1. A and B. Distribution of social support according to SS13 regarding a) Availability of Social Integration (AVSI) and b) Availability of Attachment (AVAT) in cases and controls. In b), the category "High" represents the answer "Yes" on all six questions while the category "Low" represents the answer "No" on all six questions. There were no significant differences in the distribution between cases and controls for either AVSI or AVAT.

was found to confer a significantly decreased risk of ovarian cancer. In no other subgroup was social support significantly associated with risk of ovarian cancer.

Having a large social network can of course mean a source of social support, but at the same time imply stressful expectations to support others to a higher degree. Thus, high scores at AVSI and AVAT might not per se mean low stress and a high well-being. Certainly, there are also other questionnaires than SS13 measuring various other aspects of social support and social integration, all with their pros and cons. Regarding the complex associations of self-perceived availability of social interaction and attachment in relation to stress and its biopsychosocial interaction, e.g. neuroendocrine stress hormones, these are not fully understood [6,36]. In addition, the possible links between stress, social determinants and ovarian cancer are not likely to be linear. Hence, it is a great challenge to find specific methods to measure the amount of stress related to social support and ovarian cancer.

4.1. Limitations

A main methodological consideration of the present study was the lack of registered information regarding known major risk factors related to heredity, reproduction and hormone exposure. These topics are not fully covered in the VIP questionnaire since it is primarily a cohort for health interventions regarding metabolic and cardiovascular diseases. This lack of data regarding reproductive health restricts the possibility to identify possible confounders/mediators associated with social support and risk of ovarian cancer. For example, oral contraceptive pills and high parity are known as risk-reducing factors for ovarian cancer [2]. The association between these reproductive factors and self-perceived social support would have been highly valuable to explore in this cohort.

In the VIP an abbreviated version of ISSI is used, why not all aspects of social support and interaction are covered [33,34]. Another limitation

Table 3
Low AVSI (Avalability of Social Integration) and low AVAT (Avalability of Attachment) scores according to SS13 and subsequent risk of epithelial ovarian cancer in unadjusted and adjusted conditional logistic regression analyses.

	Unadjusted analyses				Adjusted analyses[a]			
Histopathology	Cases/controls	OR	(95% CI)	*P*-value[b]	Cases/controls	aOR	(95% CI)	*P*-value[b]
AVSI								
Epithelial ovarian cancer	233/907	0.93	(0.8, 1.09)	0.38	202/765	0.85	(0.72, 1.01)	0.07
Borderline tumors	67/265	0.93	(0.7, 1.24)	0.63	59/217	0.74	(0.51, 1.07)	0.11
Invasive tumors	157/607	0.94	(0.78, 1.12)	0.49	136/518	0.89	(0.73, 1.09)	0.25
Type I[c]	38/146	0.87	(0.6, 1.26)	0.45	34/123	0.75	(0.49, 1.16)	0.20
Type II[d]	89/346	0.95	(0.74, 1.22)	0.71	75/295	0.90	(0.68, 1.19)	0.47
Serous subtype	128/500	0.87	(0.71, 1.06)	0.16	112/422	0.75	(0.59, 0.95)	0.02
Endometrioid subtype	25/93	1.23	(0.75, 2.03)	0.42	24/82	1.16	(0.65, 2.06)	0.61
Mucinous subtype	40/155	0.92	(0.64, 1.32)	0.67	33/128	0.91	(0.58, 1.43)	0.68
AVAT								
Epithelial ovarian cancer	236/923	0.78	(0.26, 2.29)	0.65	200/764	0.54	(0.16, 1.81)	0.32
Borderline tumors	69/274	0.94	(0.15, 6.06)	0.95	60/224	1.24	(0.14, 11.33)	0.85
Invasive tumors	155/603	0.73	(0.19, 2.81)	0.65	133/510	0.40	(0.09, 1.83)	0.24
Type I[c]	38/147	1.21	(0.13, 11.5)	0.87	34/124	0.62	(0.05, 8.19)	0.72
Type II[d]	87/342	0.67	(0.09, 4.81)	0.69	73/287	0.23	(0.02, 2.59)	0.23
Serous subtype	126/496	0.61	(0.12, 3.04)	0.54	110/414	0.35	(0.05, 2.23)	0.26
Endometrioid subtype	25/94	0.78	(0.07, 9.2)	0.84	24/82	0.61	(0.04, 9.24)	0.72
Mucinous subtype	41/160	1.91	(0.19, 19.36)	0.59	33/132	1.42	(0.1, 20.51)	0.80

[a] Adjusted for BMI, educational level, Cambridge Physical Activity Index, smoking status, age.
[b] A p-value < 0.5 in two-sided analyses was considered significant.
[c] Type I includes grade 1 serous tumors, grade 1 and 2 endometrioid and all invasive mucinous tumors.
[d] Type II includes grade 2 and 3 serous tumors, grade 3 endometrioid and undifferentiated tumors.

is the cross-sectional nature of the social support variables. Self-perceived social support at the day of participation in the VIP does not necessarily reflect the actual availability of social support in an attendee's life. Social support may also be inconstant and the answers in the VIP questionnaire might not specify total exposure of low or high social support at the longer term. On the other hand, the analyses of lagtime did not reveal any differences in the risk of EOC associated with social support.

4.2. Strengths

A strength of the current study is the prospective population-based nested case-control design, minimising the effect of potential recall bias and ensuring the chronology of events. The studied cohort showed similar proportions of invasive/borderline tumors, cancer site and histopathological characteristics compared to the total distribution among EOC patients in Sweden [37], and histopathological diagnoses were confirmed by pathology report review. Furthermore, known risk factors such as overweight and smoking was associated with EOC as expected [2]. Altogether, this confirms the representativeness of ovarian cancer cases as well as the validity of data in the cohort.

Social support is a complex phenomenon and there are certainly different methods to determine its influence. Since the validity and reliability of ISSI and SS13 are verified [33,38], which makes the self-assessment of availability of social support reliable, the use of this instrument could be considered adequate. Concerning prospective studies of ovarian cancer in general, the rather low incidence is a challenge. The VIP has the advantage of being population based with a high participation rate covering a wide time range. Thus, the present study fulfils the criteria for both validity and representativeness.

4.3. Conclusions

In conclusion, a general trend towards a decreased risk of ovarian cancer associated with self-perceived low social support compared to those with high self-perceived social support according to SS13 was found. Both quantitative and qualitative aspects of social support were explored. Solely the serous subtype was found to be significantly associated with low scores of availability of social interaction. In order to elucidate whether social support has an impact on the incidence of EOC, further research regarding pathophysiological mechanisms as well as epidemiological studies with repeated prospective measurements of social factors are needed.

Conflict of interest statement

The authors declare no potential conflicts of interest.

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