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Incidence and remission of urinary incontinence at midlife, a cohort study

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Objective Urinary incontinence (UI) is often considered to be an age-related disease that develops gradually as women grow older. Much remains to be learnt about factors that promote its incidence or its remission. Our objective was to assess its incidence and risk factors.

Design Longitudinal cohort study.

Setting French GAZEL cohort.

Population A cohort of 4127 middle-aged women (aged 47–52 years at baseline) over an 18-year period (1990–2008).

Methods UI was defined as 'difficulty retaining urine'. The question was asked at baseline and repeated every 3 years over an 18-year period. Two groups (UI incidence and remission) were analysed according to status at baseline (continent or incontinent). A multivariable analysis (Cox model) was used to estimate the risk factors for UI incidence and remission.

Main outcome measures Annual incidence and remission rates and risk factors for UI incidence and remission.

Results The annual incidence and remission rates for UI were 3.3% and 6.2%, respectively. High educational level (hazard ratio [HR] = 1.28; 95% confidence interval [95% CI] = 1.05–1.55), parity, i.e. at least one baby versus no baby (HR = 1.64; 95% CI = 1.19–2.27), menopause (HR = 5.44; 95% CI = 4.47–6.63), weight gain, i.e. for each kilogram change in weight (HR = 1.00; 95% CI = 1.00–1.02), onset of depressive symptoms (HR = 1.31; 95% CI = 1.09–1.57) and impairment in health-related quality of life incidence (social isolation dimension [HR = 1.29; 95% CI = 1.04–1.60] and energy dimension [HR = 1.41; 95% CI = 1.17–1.70]) were associated with an increased probability of UI. The factors associated with persistent UI were age (HR = 0.58; 95% CI = 0.55–0.61), weight gain (HR = 0.99; 95% CI = 0.98–0.99) and transition to menopausal status (HR = 1.54; 95% CI = 1.19–1.99).

Conclusions Our study suggests that, in our population of middle-aged women, age, menopause, weight gain, onset of depression and impaired health-related quality of life may promote UI.

Keywords Incidence, remission, urinary incontinence.

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Introduction

Urinary incontinence (UI) can be defined as 'the complaint of any involuntary loss of urine'.[1] The symptoms associated with UI may range from inconsequential annoyance to a debilitating disorder.[2,3] The annual direct cost of UI in the USA is estimated at $12.4 billion, a figure that exceeds the cost of breast cancer.[4]

The pathophysiological model of UI is based on a genetically predetermined functional continence reserve, which decreases with both age and injuries to the pelvic floor.[5] Epidemiological studies indicate that risk factors for UI are age, parity, previous pelvic or perineal surgery, obesity and chronic diseases.[6–11] More recently, a report that major depression may be involved in the onset of UI has opened up the field to new pathophysiological hypotheses.[12] Contrary to conventional wisdom, female hormones may impair urinary continence, as demonstrated by the prevalence of UI during pregnancy and in postmenopausal women receiving hormone replacement therapy (HRT).[13,14]. A randomised trial found that obesity is a major modifiable risk factor for UI and that weight loss leads to remission.[15]

These findings provide further evidence that an age-related and irreversible pathophysiological process is not the only explanation for UI in women.

The prevalence of UI increases with age until it peaks in midlife, between the ages of 45 and 55 years.[16] Annual rates of UI incidence vary from 1% to 11% and of UI remission from 5% to 11%.[17–24]

Most studies assessing the causes of UI are cross-sectional and therefore cannot assess UI as a dynamic condition. Moreover, the few longitudinal studies have had relatively limited follow-ups (2–5 years) or no interval evaluation of the UI evolution during the study period.[25] Longitudinal studies are essential for the elucidation of the natural history of UI by clarifying the temporal relations and directions of the risk factors suggested by cross-sectional studies.[26] Long-term cohort studies also provide better evidence of causality. That is, in long-term studies, it is possible to demonstrate that the presumed cause actually precedes the effect, which is impossible in a cross-sectional study.

The aim of our study was to analyse the factors related to the incidence and remission of UI in a cohort of women aged between 47 and 52 years at study entry and followed for 3–18 years, whilst taking into account not only the factors traditionally studied, but also social characteristics and physical and mental health.

Methods

Our population belongs to the French GAZEL cohort (http://www.gazel.inserm.fr/), which began in 1990 and includes 20 000 men and women who then worked for the French national power company (EDF-GDF) and volunteered to participate in an epidemiological research programme coordinated by INSERM (Institut National de la Santé et de la Recherche Médicale).

Women in the GAZEL cohort, aged 45 years and over, were included in a specific prospective longitudinal survey, the 'Women and their Health' study (n = 4127). Its main objective is to study women's health as they reach the menopause and afterwards.[27] These women received a general health questionnaire each year as part of the overall GAZEL survey and an additional questionnaire specific to women's health issues every 3 years (1990–2008). This specific questionnaire first included a question about UI: 'Avez-vous des difficultés à retenir vos urines?'. This can be translated as: 'Do you have trouble holding your urine?'. A positive answer defined UI.

Women were categorised with incident incontinence the first time they answered 'yes' to the question about UI asked in each triennial questionnaire. All women with more than two answers to this question ('Do you have trouble holding your urine?') were included in the study. Women with incontinence were defined as in remission the first time after their initial 'yes' that they answered 'no' to the question about UI.

The covariables considered were as follows:

1 sociodemographic factors, including age at inclusion, occupation, mean household income, educational level, marital status, heavy lifting at work and place of residence;
2 lifestyle factors, such as alcohol consumption, smoking habits and physical activity;
3 medical and psychological factors were assessed at cohort entry and at every follow-up; they included weight (i.e. for each kilogram change in weight), body mass index (BMI), overweight (BMI $\geq$ 25 kg/m^2), obesity (BMI $\geq$ 30 kg/m^2), medical history (high blood pressure and diabetes), major depression (defined by a Center for Epidemiologic Studies Depression Scale [CES-D] score of $\geq$23), overall health status (score assessed according to the answer to the question, 'How do you judge your overall health', on a scale of 1–8) and quality of life (QoL) (measured with the scores of the six dimensions of the Nottingham Health Profile [NHP]: physical mobility, social isolation, emotional reactions, pain, sleep and energy; QoL NHP scores > 0 were considered to be impaired, QoL NHP scores = 0 were considered to be unimpaired).
4 gynaecological and obstetric history, including parity (i.e. at least one baby versus no baby), types of delivery (caesarean, vaginal, operative/instrumental vaginal) and, at baseline and each follow-up, menopausal status, hormone therapy (HRT) and hysterectomy.

Among these covariables, those recorded during follow-up were taken into account into the regression model (s) as time-dependent variables in two different ways:[28]

1 as binary time-dependent variables with a single change in the exposure value before the event or censoring;
2 continuous time-dependent variables with multiple (i.e. updated) changes in the exposure value during follow-up until the event or censoring (weight).

Statistical analysis was performed with SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). We used the Kaplan–Meier method to estimate the cumulative probabilities of UI incidence and remission and to present them graphically. A Cox model was used for the univariable analysis of predictive factors of incidence and remission. The multivariable analysis was conducted with a semi-parametric Cox model. The hypotheses underlying this model, log-linearity and proportional hazards, were checked. Only variables significant at 20% in the univariable analysis (log-rank test or Wald test) were included in the final model.

Results

Follow-up was available for 3828 women. The final sample for the analysis of UI incidence included 2887 women and that for UI remission 941 women, according to their urinary continence at baseline (Figure 1).

The median follow-up was 12 years (range, 3–18 years; interquartile range [IQR], 7–16 years). The annual incidence rate of UI was 3.3% and the annual remission rate was 6.2%.

Table 1 summarises the population's characteristics. The median age of the 3828 women included in the population was 47 years (IQR, 46–50 years) at baseline and 58 years (IQR, 57–64 years) at the end of follow-up.

Their median weight at baseline was 58 kg (IQR, 54–63 kg). The median weight gain during follow-up was 3 kg (IQR, 0–7 kg). At baseline, 33% had a CES-D score of 23 or above, reflecting the existence of depressive symptoms. Moreover, 29% of women met the CES-D criteria for depression on the annual questionnaire 1 year before the report of UI on the women's health questionnaire collected every 3 years. Impaired QoL on the annual questionnaire 1 year before the report of UI on the women's health questionnaire collected every 3 years was more frequent for all dimensions of NHP in the remission group than in the incidence group. At baseline, 27.7% of women were postmenopausal, and 40.8% reached the menopause before the event. A hysterectomy preceded the event or censoring for 17.6%.

Table 2 presents the results of the univariable analysis measuring the association between UI incidence and remission and the women's general health characteristics. A 1-kg weight gain in the year preceding the event, overweight, obesity, impaired QoL and depression were significantly associated with UI incidence. Weight gain, hypertension, obesity and the deterioration of QoL (in its emotional and pain dimensions) were significantly associated with lower rates of UI remission.

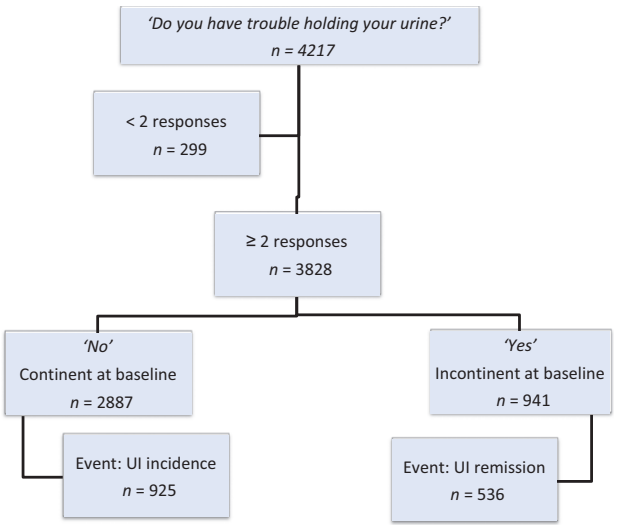

Figure 1. Flow chart.

Table 1. Demographic characteristics

Characteristic	No UI at baseline (n = 2887) n Mean [±SD]	UI at baseline (n = 941) n Mean [±SD]
Age at baseline (years)	2887 47.73 [±0.06]	941 47.87 [±0.07]
Weight at baseline (kg)	2884 58.39 [±0.21]	940 60.75 [±0.26]
Weight* (kg)	2884 64.40 [±0.67]	940 66 [±0.84]
BMI at baseline (kg/m^2)	2844 22.38 [±0.08]	927 23.09 [±0.11]
BMI* (kg/m^2)	2851 24.18 [±0.22]	928 25.08 [±0.27]
	n (%)	n (%)
High school diploma		
No	2154 (77.15)	703 (78.20)
Yes	638 (22.85)	196 (21.80)
Household monthly income		
<1982€	523 (23.67)	175 (24.86)
1982–3810€	1135 (51.35)	377 (53.55)
>3810€	552 (24.98)	152 (21.59)
Marital status		
Alone	399 (15.17)	143 (16.25)
Couple	2231 (84.83)	737 (83.75)
Place of residence		
Rural	443 (17.20)	180 (21.85)
Urban	2132 (82.80)	640 (78.05)
Occupation		
Management or training	263 (9.40)	69 (7.48)
Supervisors, sales representatives	1746 (62.38)	560 (60.74)
Blue collar, clerical staff	790 (28.22)	293 (31.78)
Heavy lifting at work		
No	721 (71.60)	186 (61.79)
Yes	286 (28.40)	115 (38.21)
Regular physical exercise (>1 per week)		
Yes	990 (34.83)	287 (30.93)
No	1852 (65.17)	641 (69.07)
Smoking		
Nonsmoker	1927 (67.57)	626 (67.38)
Ex-smoker	581 (20.37)	177 (19.05)
Current smoker	344 (12.06)	126 (13.56)
Alcohol		
Never	134 (4.64)	40 (4.25)
Occasionally	2430 (84.17)	769 (81.72)
Daily	323 (11.19)	132 (14.03)

BMI, body mass index; SD, standard deviation; UI, urinary incontinence.
*Time-dependent covariate with multiple changes.

Table 2. Physical characteristics

Characteristic	No UI at baseline (*n* = 2887) *n* (%)	UI at baseline (*n* = 941) *n* (%)
Diabetes		
Yes	76 (3.21)	44 (5.62)
No	2289 (96.79)	739 (94.38)
High blood pressure		
Yes	513 (21.68)	202 (25.80)
No	1853 (78.32)	581 (74.20)
Depressive disorder (CES-D ≥ 23) (at baseline)		
No	1839 (67.02)	498 (55.33)
Yes	905 (32.98)	402 (44.67)
Depressive disorder (CES-D ≥ 23)*		
No	1793 (71.01)	478 (62.16)
Yes	732 (28.99)	291 (37.84)
NHP physical mobility*		
0	1853 (64.65)	466 (50.0)
>0	1013 (35.35)	466 (50.0)
NHP social isolation*		
0	2124 (74.42)	592 (63.52)
>0	730 (25.58)	340 (36.48)
NHP emotional reaction*		
0	1159 (54.63)	411 (44.10)
>0	1295 (45.37)	521 (55.90)
NHP pain*		
0	1702 (59.64)	413 (44.31)
>0	1152 (40.36)	519 (55.69)
NHP sleep*		
0	1302 (45.62)	353 (37.88)
>0	1552 (54.38)	579 (62.12)
NHP energy*		
0	1881 (65.91)	469 (50.32)
>0	973 (34.09)	463 (49.68)
Hysterectomy		
No	2415 (83.65)	741 (78.75)
Yes	472 (16.35)	200 (21.25)
Urinary incontinence surgery		
No	563 (86.62)	203 (70.98)
Yes	87 (13.38)	83 (29.02)
Pelvic organ prolapse surgery		
No	568 (88.47)	208 (73.76)
Yes	74 (11.53)	74 (26.24)
Menopause (at baseline)		
No	2077 (72.95)	647 (70.48)
Yes	770 (27.05)	271 (29.52)
Menopause**		
No	1636 (56.69)	628 (66.74)
Yes	1250 (43.31)	313 (33.26)
HRT at baseline		
Non-menopausal	2077 (71.94)	647 (68.76)
Menopause without HRT	279 (9.66)	119 (12.65)
Menopause with HRT	531 (18.39)	175 (18.60)
HRT**		
Non-menopausal	1636 (56.66)	628 (66.74)
Menopause without HRT	337 (11.67)	81 (8.61)
Menopause with HRT	914 (31.67)	232 (24.65)
Parity		
0	368 (12.84)	67 (7.15)
1	820 (28.60)	223 (23.80)
2	1440 (50.23)	544 (58.06)
≥3	239 (8.34)	103 (10.99)
Caesarean section		
No	1543 (89.71)	539 (92.45)
Yes	177 (10.29)	44 (7.55)
Instrumental extraction		
No	1389 (81.71)	454 (79.23)
Yes	311 (18.29)	119 (20.77)

CES-D, Center for Epidemiologic Studies Depression Scale; HRT, hormone replacement therapy; NHP, Nottingham Health Profile; UI, urinary incontinence.
*Time-dependent covariate with multiple changes.
**Time-dependent covariate at unique change.

Factors significantly associated with an increased incidence of UI were parity (having no children appeared to be protective against UI, and the delivery of at least two children appeared to increase UI incidence). A hysterectomy and reaching menopause during follow-up were also associated with UI incidence. Menopause was the only characteristic significantly associated with a lower rate of UI remission (i.e. meeting the definition of menopausal increased the risk of persistent UI).

In the multivariable analysis, the factors significantly associated with UI incidence were a higher educational level (hazard ratio [HR] = 1.28; 95% confidence interval [95% CI] = 1.05–1.55), weight gain (HR = 1.00; 95% CI = 1.00–1.02; per kg), depressive symptoms (HR = 1.31; 95% CI = 1.09–1.57), impaired QoL (in the energy [HR = 1.41; 95% CI = 1.17–1.70] and social isolation [HR = 1.29; 95% CI = 1.04–1.60] dimensions), multiparity (HR = 1.64; 95% CI = 1.19–2.27) and menopause (HR = 5.44; 95% CI = 4.47–6.63) (Table 3). The factors associated with a lower chance of UI remission were age (HR = 0.58; 95% CI = 0.55–0.61; per year) and overweight (HR = 0.99; 95% CI = 0.98–0.99; per kilogram). Reaching menopause during follow-up was associated with a higher probability of UI remission (HR = 1.54; 95% CI = 1.19–1.99) (Table 4).

Discussion

Main findings

The annual rate of UI incidence in our population was 3.3%, and that of remission was 6.2%. Factors associated

Table 3. Association between women's characteristics and incidence of urinary incontinence. Multivariate analysis

Women's characteristics	HR	95% CI	*P*
High school diploma	1.28*	1.05–1.55	0.01*
Marital status: married, living as	1.11	0.89–1.38	0.37
Alcohol			
Occasionally	1.18	0.78–1.79	0.65
Daily	1.11	0.70–1.76	
Weight**	1.01*	1.00–1.02	0.01*
Depressive disorder (CES-D ≥ 23)**	1.31*	1.09–1.57	0.01*
NHP physical mobility > 0**	1.17	0.98–1.41	0.08
NHP social isolation > 0**	1.29*	1.04–1.60	0.02*
NHP emotional reaction > 0**	0.97	0.79–1.20	0.81
NHP pain > 0**	0.93	0.77–1.11	0.40
NHP sleep > 0**	0.93	0.78–1.11	0.42
NHP energy > 0**	1.41*	1.17–1.70	<0.01*
Nulliparity	0.61*	0.44–0.84	<0.01*
Menopause***	5.44	4.47–6.63	<0.01*
Hysterectomy***	0.81	0.66–1.01	0.06

CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; HR, hazard ratio; NHP, Nottingham Health Profile.
**P*-value < 0.05.
**Time-dependent covariate with multiple changes.
***Time-dependent covariate at unique change.

Table 4. Association between women's characteristics and remission of urinary incontinence. Multivariate analysis

Women's characteristics	HR	95% CI	*P*
Age	0.58	0.55–0.61	<0.0001*
Weight**	0.99	0.98–0.99	0.03*
Depressive disorder (CES-D ≥ 23)**	1.03	0.81–1.31	0.75
NHP physical mobility > 0**	0.90	0.69–1.17	0.45
NHP social isolation > 0**	0.91	0.68–1.22	0.52
NHP emotional reaction > 0**	0.89	0.68–1.17	0.40
NHP pain > 0**	0.89	0.69–1.15	0.37
NHP energy > 0**	1.10	0.85–1.42	0.46
High school diploma	1.26	0.97–1.64	0.08
Urban place of residence	1.09	0.83–1.44	0.52
Regular physical exercise (>1 per week)	0.86	0.68–1.09	0.22
High blood pressure	0.95	0.72–1.27	0.74
Menopause***	1.54	1.19–1.99	<0.01*

CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; HR, hazard ratio; NHP, Nottingham Health Profile.
**P*-value < 0.05..
**Time-dependent covariate with multiple changes.
***Time-dependent covariate at unique change.

with UI incidence were social (educational level), obstetric (parity) and hormonal (menopause); UI incidence was also related to health status (weight gain, onset of depressive symptoms and deteriorating QoL). The only factors associated with the persistence of UI were ageing and weight gain. Menopause onset was positively associated with UI remission.

Strengths and limitations

The mean duration of follow-up exceeded 12 years in both groups (incidence and remission). Moreover, because the GAZEL cohort is a generalist cohort, it contains data for studying numerous health characteristics. Using a survival model to analyse UI incidence and remission allowed us to consider changes over time in some risk factors for UI onset or remission, such as weight and hormonal status. In addition to the survival analysis, using age as a time scale can make it easier to interpret the roles of other risk factors, whether (e.g. hormonal status) or not (e.g. weight and parity) they are directly related to age.[29] Our study was based on a different definition of UI than that of the International Continence Society in 2003.[1] Several studies[12,20,30,31] have nonetheless used definitions similar to ours, and our annual rates of incidence and remission are similar to those in the literature. However, this difference in definition may lead to misclassification.

Moreover, the 'Women and their Health' cohort was developed to analyse health events around the menopause. It therefore collected less precise data than a specific cohort focused on UI. Remission was defined only as a complete remission of all symptoms. Some risk factors, such as birthweight, episiotomy, antenatal incontinence and perineal pelvic floor training, were not available for all women and were therefore not considered in our analyses, although they may be considered later.

Interpretation

Longitudinal studies are essential to elucidate the natural history of UI by clarifying the temporal relations and directions of the risk factors suggested by cross-sectional studies. The former also provide better evidence of causality for risk factors than do cross-sectional studies. That is, in a long--term cohort study, it is possible to demonstrate that the presumed cause actually precedes the effect, which is of course impossible in a cross-sectional study.

In our study, the association of ageing with a lower likelihood of remission confirms findings from recent series.[17,32] We found that, even among middle-aged women, nulliparity was negatively associated (HR = 0.68; 95% CI = 0.49–0.95) with UI incidence. The effect of parity on this incidence appears to be delayed for many years after last delivery, as we observed that the delivery of at least one child was associated with an increased risk of *de novo* UI, long after childbirth. It may therefore be hypothesised that pregnancy and childbirth may lead to the onset of UI several years after the initial trauma. We observed that a

weight gain of 1 kg was significantly associated with a higher incidence of UI (HR = 1.01; 95% CI = 1.00–1.02). This result confirms the results of other cohort studies.[33,34] Weight gain was also inversely correlated with UI remission, and thus confirmed the findings from a recent randomised trial in which weight loss reduced the frequency of UI episodes.[15] Studies of the link between pathophysiological disturbances of the pelvic floor and overweight suggest that excess weight may act through an increase in intra-abdominal pressure, which then causes an overactive bladder[35] and increased urethral mobility.[36]

The onset of menopause in our sample was strongly associated with the onset of UI, but also with its disappearance. The role of hormonal factors associated with the menopausal transition in pelvic floor disorders is controversial.[11] UI in women during the menopause might be explained by oestrogen deficiency, which would imply urogenital tissue fragility.[37] Accordingly, the findings reported by the Women's Health Initiative (WHI) were rather unexpected. In this study of 27 347 postmenopausal women, the administration of oestrogen without progestin among women without incontinence at baseline was associated with an increased risk at 1 year of all types of UI, and with increased UI severity among women incontinent at baseline. In women receiving oestrogen plus progestin, the risk of mixed and stress UI increased at 1 year, but the risk of urge UI did not.

In a longitudinal study, Waetjen et al.[38] reported that it appears to be incorrect to attribute the worsening of UI symptoms observed in the early perimenopause to the menopausal transition; although the risk of developing UI is indeed higher in the perimenopausal and postmenopausal periods, this change can be attributed to weight gain during this period.

The incidence of stress UI is known to decrease among women older than 55 years. In contrast, however, the incidence of urgency incontinence increases with age. In our population, the paradoxical role of menopause, associated with both UI incidence and UI remission, might be explained by different proportions of stress and urgency incontinence in the two samples. As we stated earlier, our data are not sufficiently precise to differentiate between these two types of UI, and we cannot verify the assumption that menopause may be associated with the incidence of urgency incontinence and the remission of stress incontinence. The role of oestrogen deficiency is especially difficult to interpret in our study because most of the postmenopausal women in the GAZEL cohort took HRT.[27] The effect of menopause here may thus be caused more by the effect of HRT, which acts differently on stress than on urgency incontinence. The WHI found that systemic HRT affected the risk of UI, especially stress UI (odds ratio [OR] between 1.87 and 2.15), but also, although less significantly, urgency incontinence (OR between 1.15 and 1.32).[13] In contrast, oestrogens administered topically promote UI remission, improving both frequency and urgency incontinence.[39]

We observed that depressive symptoms were significantly associated with the incidence of UI (HR = 1.30; 95% CI = 1.09–1.56). Several cross-sectional studies have reported this association, but were unable to clarify the issue of temporality. Our longitudinal study, which used survival analysis and took the time-dependent variables into account, thus confirms the link between major depression at baseline and the subsequent onset of UI, observed by Melville et al.[12] We found that depressive symptoms clearly preceded UI onset.

Several mechanisms may explain this observation. Serotonin is involved in the inhibition of voiding reflex arcs and stimulation of the closure of the urethra.[12] Thus, impairment of the serotonergic pathway might explain both depression and UI, as well as the reported efficacy of duloxetine in treating UI.[40]

Another pathophysiological assumption is that an overactive sympathetic nervous system, responsible for depressive symptoms, might act on the bladder control system. Finally, this effect may be related to the fact that depressed women are more likely to perceive changes in their health.[27]

Impairment of the NHP dimensions of social isolation and energy preceded the onset of urinary problems in our study. However, the factors that make up these two NHP dimensions relate, in part, to problems that can be considered as depression. Accordingly, confounding with depression cannot be excluded, although the multivariable analysis confirms the role of these two dimensions after adjustment for depressive symptoms. QoL did not affect UI remission in our populations. Future research should investigate the treatment of depression and its effects on UI.

Conclusions

UI is a dynamic phenomenon, and longitudinal studies, with a relatively long follow-up, are necessary to characterise its risk factors accurately. The originality of this study is that it clarifies the factors related to UI incidence and remission in midlife women over a long follow-up period. Weight is confirmed as the major modifiable risk factor of UI, indeed, the only modifiable factor clearly identified. Clinicians should be aware of recent findings about factors such as depression, as they raise the possibility of new medical or behavioural therapies.

Disclosure of interests

None.

Contribution to authorship

GL, VR and XF were implicated in the concept and design, analysis and interpretation of the data and the writing of the manuscript. HP was implicated in the statistical analysis. MZ was implicated in the revision of the manuscript.

Details of ethics approval

The GAZEL project received the approval of the National Council of the College of Physicians and the National Consultative Ethics Committee for Life Sciences and Health. GAZEL # 105 728 – 26.04.1988.

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