Elena Toffol

Mental health and reproductive health in women

RESEARCH

The epidemiology and phenomenology of many psychiatric disorders differ between genders. It is plausible that (endogenous and exogenous) gonadal hormones and reproductive events contribute to this pattern.

This work investigated the relationship between mental health and psychological well-being in relation to reproductive features of women who participated in two Finnish population-based studies (Health 2000 and FINRISK 1997, 2002 and 2007).

A miscarriage as a pregnancy outcome resulted related to a high prevalence of depressive disorders, and to more severe depressive or anxiety symptoms compared with other pregnancy outcomes. Moreover, the higher the number of miscarriages was, the worse the current state of mood was and the higher the frequency of a psychiatric diagnosis. The use of hormonal contraception was not associated with adverse psychological status or depressive symptoms or disorders, and no effect of different hormonal compounds was detected. Finally, a high prevalence of depressive and anxiety disorders emerged in connection with the menopausal transition, and current use of hormone therapy was associated with worse psychological well-being or mental health in perimenopausal and postmenopausal women.

In general, psychological well-being and mental health seem to be related to reproductive events in women.

NATIONAL INSTITUTE
FOR HEALTH AND WELFARE

National Institute for Health and Welfare
P.O. Box 30 (Mannerheimintie 166)
FI-00271 Helsinki, Finland
Telephone: 358 29 524 6000
www.thl.fi

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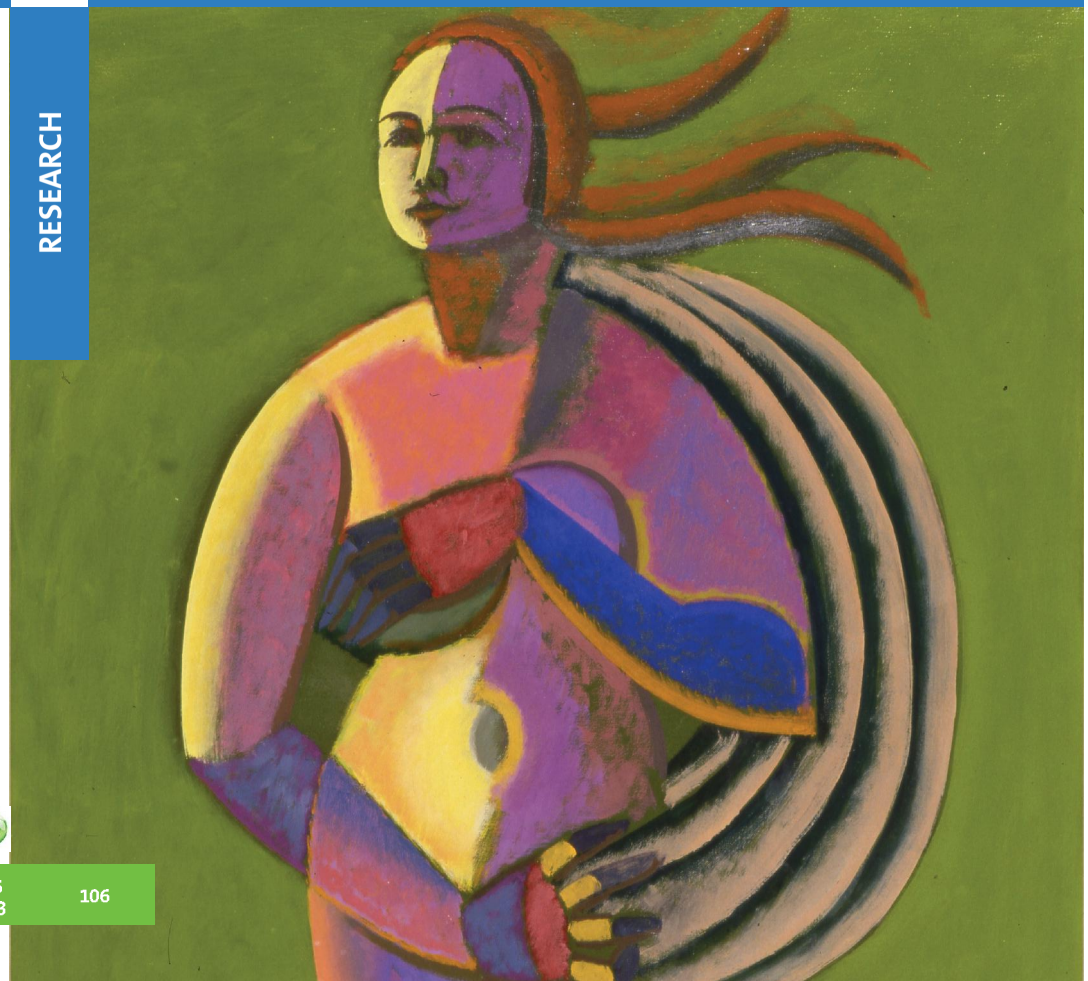

RESEARCH NR 106 ♦ 2013

Elena Toffol

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ACADEMIC DISSERTATION

To be publicly discussed with the permission of the Faculty of Medicine, University of Helsinki, Finland, at the Christian Sibelius auditorium, Välskärinkatu 12, on June 7th 2013, at 12 noon

National Institute for Health and Welfare
Department of Mental Health and Substance Abuse Services
and
University of Helsinki
Department of Psychiatry

Helsinki, Finland 2013

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Supervisors:
Research Professor Timo Partonen
National Institute for Health and Welfare,
Department of Mental Health and Substance Abuse Services
Helsinki, Finland

Docent Jari Haukka
University of Helsinki, Hjelt Institute, and
National Institute for Health and Welfare,
Department of Mental Health and Substance Abuse Services
Helsinki, Finland

Professor Jouko Lönnqvist
National Institute for Health and Welfare,
Department of Mental Health and Substance Abuse Services, and
University of Helsinki, Department of Psychiatry
Helsinki, Finland

Thesis committee:
Docent Oskari Heikinheimo
University of Helsinki and Helsinki University Central Hospital
Department of Obstetrics and Gynecology
Helsinki, Finland

Doctor Taina Hätönen
Finnish Student Health Service, and
Helsinki University Central Hospital, Department of Psychiatry, and
National Institute for Health and Welfare,
Department of Mental Health and Substance Abuse Services
Helsinki, Finland

Reviewers:
Professor Hannu Koponen
Kuopio University Hospital, Department of Psychiatry, and
University of Eastern Finland, Faculty of Health Sciences,
Institute of Clinical Medicine, Department of Psychiatry
Kuopio, Finland

Docent Soili Lehto
University of Eastern Finland, Faculty of Health Sciences,
Institute of Clinical Medicine, Department of Psychiatry
Kuopio, Finland

Opponent:
Professor Jerker Hetta
Karolinska Institute, Department of Clinical Neuroscience
Stockholm, Sweden

To men and women

Abstract

Elena Toffol. Mental health and reproductive health in women. National Institute for Health and Welfare (THL). Research 106. 136 pages. Helsinki, Finland 2013.
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This research aims at studying the relationship between mental health and reproductive features in women. The epidemiology and phenomenology of many psychiatric disorders differ between genders, with depressive and anxiety disorders, as well as attempted suicide, being more common in women, and completed suicide, personality disorders and substance use disorders, in men. It is plausible that (endogenous and exogenous) gonadal hormones and reproductive events contribute to this pattern.

Data on women who participated in two Finnish population-based studies (Health 2000 and FINRISK 1997, 2002 and 2007) were analyzed. Data were collected through face-to-face interviews, self-administered questionnaires and health examinations. Different structured (BDI-21, BDI-13, GHQ-12, CIDI) and non-structured tools were used to assess mental health and psychological well-being. Study I focused on the association between mental health and miscarriage, by history and number; Studies II and III focused on the relationship with use of hormonal contraception (either oral or intrauterine) and its duration; Study IV concentrated on the associations between mental health and hormone therapy in perimenopausal and postmenopausal women.

Study I showed that a miscarriage as a pregnancy outcome was related to a high prevalence of depressive disorders, and to more severe depressive or anxiety symptoms compared with other pregnancy outcomes. Moreover, the higher the number of miscarriages was, the worse the current state of mood was and the higher the frequency of a psychiatric diagnosis.

Studies II and III revealed that the use of hormonal contraception was not associated with adverse psychological status or depressive symptoms/disorders. Additionally, no effect of different hormonal compounds was detected.

The main finding in Study IV was the high prevalence of depressive and anxiety disorders among women in connection with the menopausal transition. Moreover, in this group, an association between current use of hormone therapy and worse psychological well-being or mental health was detected.

The results of this study support the hypothesis of an association between psychological well-being and reproductive features in women. The importance of considering reproductive health and events when assessing psychological status and mental health in women is discussed.

Keywords: mental health, depression, anxiety, women, reproduction, miscarriage, hormonal contraception, hormone therapy.

Tiivistelmä

Elena Toffol. Mental health and reproductive health in women. [Naisten mielenterveys ja lisääntymisterveys] Terveyden ja hyvinvoinnin laitos (THL). Tutkimus 106. 136 sivua. Helsinki, Finland 2013.
ISBN 978-952-245-897-1 (painettu); ISBN 978-952-245-898-8 (pdf)

Tässä tutkimuksessa tarkastellaan naisten mielenterveyden ja lisääntymisterveyden välistä suhdetta. Monet psykiatriset sairaudet ja oireet ilmenevät eri lailla sukupuolten välillä, esimerkiksi masennustila ja ahdistusoireet ovat yleisempiä naisilla, kun sitä vastoin itsemurhat sekä persoonallisuus- ja päihdehäiriöt ovat yleisempiä miehillä. On todennäköistä, että sukurauhashormonit ja lisääntymistapahtumat vaikuttavat mielenterveydessä ilmeneviin eroihin.

Naisten tutkimusaineistona käytettiin kahta suomalaista väestötutkimusta (Terveys 2000 ja FINRISK 1997, 2002, 2007). Tämä aineisto koostui henkilökohtaisista haastatteluista, kyselylomaketiedoista ja terveystarkastusmittauksista. Mielenterveyden ja hyvinvoinnin arvioinnissa käytettiin sekä strukturoituja (BDI-21, BDI-13, GHQ-12, CIDI) että ei-strukturoituja menetelmiä. Ensimmäinen tutkimus koski mielenterveyden ja keskenmenojen sekä niiden määrän välistä suhdetta. Toisessa ja kolmannessa tutkimuksessa tarkasteltiin mielenterveyden ja hormonaalisten (suun kautta nautittavien tai kohdunsisäisten) ehkäisykeinojen käytön sekä ehkäisyn keston välistä suhdetta. Neljäs tutkimus keskittyi mielenterveyden ja hormonikorvaushoidon välisiin yhteyksiin vaihdevuosi-ikäisillä ja vanhemmilla naisilla.

Ensimmäinen tutkimus osoitti että keskenmenon kokeneilla masennus oireet ja häiriöt olivat yleisiä. Tämän lisäksi keskenmeno yhdistyi vakavampiin mielenterveyden häiriöihin verrattuna muihin raskauden lopputuloksiin. Mitä enemmän keskenmenoja oli, sitä todennäköisempiä olivat psyykkiset oireet tai mielenterveyden häiriöt.

Toinen ja kolmas tutkimus osoittivat, että hormonaalisen ehkäisyn käyttö ei ollut yhteydessä psyykkiseen pahoinvointiin tai masennusoireisiin. Eri hormoniyhdisteet eivät tässä suhteessa eronneet toisistaan.

Neljännen tutkimuksen päälöydös oli se, että masennus- ja ahdistuneisuushäiriöt olivat yleisiä vaihdevuosi-ikäisillä naisilla. Lisäksi tässä ryhmässä hormonikorvaushoidon käyttö oli yhteydessä psyykkiseen pahoinvointiin.

Tämän tutkimuksen tulokset tukevat hypoteesia, että naisten lisääntymisterveys vaikuttaa psyykkiseen hyvinvointiin. Lisääntymisterveyttä edistämällä voidaan mahdollisesti edistää myös mielenterveyttä.

Avainsanat: mielenterveys, masennus, ahdistus, naiset, lisääntymisterveys, keskenmeno, hormonaalinen ehkäisy, hormonihoito.

Riassunto

Elena Toffol. Mental health and reproductive health in women. [Salute mentale e salute riproduttiva nella donna]. Terveyden ja hyvinvoinnin laitos (THL). Ricerca 106. 136 pagine. Helsinki, Finlandia 2013.
ISBN 978-952-245-897-1 (formato cartaceo); ISBN 978-952-245-898-8 (formato pdf)

Lo scopo di questo studio è di esaminare la relazione tra salute mentale e caratteristiche riproduttive nella donna. L'epidemiologia e la fenomenologia di molti disturbi psichiatrici è significativamente diversa tra uomo e donna. In particolare, la prevalenza dei disturbi depressivi e d'ansia, così come dei tentativi di suicidio, è più elevata tra le donne; d'altra parte, il suicidio, ma anche i disturbi di personalità e i disturbi da uso di sostanze, sono più comuni tra gli uomini. Si può ipotizzare che queste differenze di genere siano correlate all'influenza degli ormoni gonadici (sia endogeni che esogeni) e agli eventi connessi alla riproduzione.

In questa ricerca si sono analizzati i dati raccolti in Finlandia nel corso di due studi di popolazione (Health 2000 e FINRISK 1997, 2002 e 2007). I dati sono stati raccolti attraverso questionari auto- ed etero-somministrati, interviste vis-à-vis e visite mediche. Il benessere psicologico e la salute mentale sono stati esaminati utilizzando strumenti di valutazione strutturati (BDI-21, BDI-13, GHQ-12, CIDI) e non strutturati. Lo Studio I si è focalizzato sull'associazione tra salute mentale e presenza in anamnesi di aborto spontaneo, singolo o multiplo. Gli Studi II e III si sono occupati della relazione tra salute mentale o benessere psicologico, e uso di contraccettivi ormonali (orali e/o intrauterini) e sua durata; lo Studio IV si focalizza sull'associazione con l'impiego di terapia ormonale sostitutiva in peri- e post-menopausa.

I risultati dello Studio I hanno rivelato che l'aver un aborto spontaneo in anamnesi si associava con una maggior prevalenza, rispetto ad altri esiti di gravidanza, di sintomi e disturbi depressivi ed ansiosi. Sono inoltre emersi un peggioramento dell'umore ed una maggior frequenza di diagnosi psichiatriche all'aumentare del numero di aborti spontanei.

Gli Studi II e III hanno evidenziato che l'uso di contraccettivi ormonali non è associato ad un peggior stato di benessere psicologico né ad un aumentato rischio di manifestare sintomi e/o disturbi depressivi. Anche la valutazione dei diversi composti non ha evidenziato differenze significative.

Il principale risultato dello Studio IV è l'elevata prevalenza di disturbi depressivi ed ansiosi durante il periodo di transizione menopausale. In questo studio l'uso attuale di una terapia ormonale sostitutiva è risultato associato con una maggior compromissione della salute mentale, nonché con un peggior stato di benessere psicologico in generale.

I risultati di questa ricerca sono in linea con l'ipotesi iniziale, ovvero dell'esistenza di un'associazione tra benessere psicologico e caratteristiche riproduttive nella donna. Alla luce di questi risultati si è ribadita l'importanza di effettuare un'attenta valutazio-

ne della salute riproduttiva in generale e degli eventi della vita riproduttiva in particolare ad ogni donna che manifesti sintomi o disagio psicologico.

Parole chiave: salute mentale; depressione; ansia; donne; riproduzione; aborto spontaneo; contraccezione ormonale; terapia ormonale sostitutiva.

Contents

List of original publications

This thesis is based in the following original publications, which are referred to in the text by Roman numerals:

I Toffol E, Koponen P, Partonen T. Miscarriage and mental health: results of two population-based studies. Psychiatry Res 2013; 205(1–2): 151–158.

II Toffol E, Heikinheimo O, Koponen P, Luoto R, Partonen T. Hormonal contraception and mental health: results of a population-based study. Hum Reprod 2011; 26(11): 3085–3093.

III Toffol E, Heikinheimo O, Koponen P, Luoto R, Partonen T. Further evidence for lack of negative associations between hormonal contraception and mental health. Contraception 2012; 86(5): 470–480.

IV Toffol E, Heikinheimo O, Partonen T. Associations between psychological well-being, mental health and hormone therapy in peri- and postmenopausal women: results of two population-based studies. Menopause 2012; doi: 10.1097/gme.0b013e318278eec1.

Abbreviations

BDI	Beck Depression Inventory
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
COC	Combined Oral Contraceptive
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EPT	Estrogen Progestin Therapy
ET	Estrogen Therapy
FSH	Follicle Stimulating Hormone
GAD	Generalized Anxiety Disorder
GHQ	General Health Questionnaire
HT	Hormone Therapy
IUD	Intrauterine Device
LH	Luteinizing Hormone
LNG-IUS	Levonorgestrel Intrauterine System
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
NS	Non Significant
OC	Oral Contraceptive
OCD	Obsessive Compulsive Disorder
OR	Odds Ratio
PMDD	Premenstrual Dysphoric Disorder
PMS	Premenstrual Syndrome
PTSD	Post-Traumatic Stress Disorder
SD	Standard Deviation

1 Introduction

A marked gender difference exists in the epidemiology and phenomenology of many psychiatric disorders. In particular, mood and anxiety disorders are known to be more common (and more commonly reported) in women than in men (Kuehner, 2003; Wittchen et al., 2011). This is especially true in the period of time that encompasses the fertile life of women, i.e. from the menarche to the menopausal transition. A specific gender and age pattern does also exist for suicidal behavior, with completed suicide being more common among old men, and attempted suicide among young women (Hawton, 2000).

A complex interaction between multiple factors, including individual personality traits, social background, culture and, not least, biology, is required to explain this phenomenon. Among others, hormones play an important role. In spite of a wide variety of hormones that are known to impact on mental health (e.g., cortisol and thyroid hormones), the influence of gonadal hormones on mental health and psychological well-being in general is not fully understood. However, given the multiple effects that estrogens and progesterone exert on the central nervous system from the fetal stage onward, it is plausible that they at least contribute to the etiology, phenomenology and epidemiology of psychiatric disorders.

Compared to men, women exhibit marked fluctuations in the levels of gonadal hormones during their fertile life. In addition, since reproductive events are so obviously connected with social, psychological and physiological phases in women, it is important to understand the relationship between mental health, gonadal hormones and reproductive events.

Reproductive events include puberty, menstrual cycle, pregnancy and menopause, but also pregnancy outcomes such as spontaneous and induced abortions, and exogenous gonadal hormones in the form of hormonal contraception and hormone replacement therapy. It is reasonable to assume that all these are able to influence women's mental health, both because of their psychological and social significance, as well as because of their biological effects on the central nervous system.

The social, psychological and biological effects of the above-mentioned factors can not be clearly disentangled. Nevertheless, trying to understand the way reproductive life is related to mental health and psychological well-being is a preliminary step to further investigating the underlying mechanisms that regulate such a complex association.

This is particularly meaningful nowadays, when depressive and anxiety disorders that are more prevalent in women have an increasing social and economic impact (WHO, 2008).

2 Review of the literature

2.1 Psychopathology: gender differences in epidemiology and phenomenology

A significant proportion of psychiatric disorders are more prevalent in women than in men (Wittchen et al., 2011). The main exceptions are substance use disorders, psychotic disorders and personality disorders, which are more common in men. Gender differences also exist with regard to the clinical presentation, treatment response and outcome of several mental disorders (Table 1).

2.1.1 Mood disorders in women: epidemiology and phenomenology

A recent study that sought to establish the 12-month prevalence of mental disorders in Europe found depression to be the most relevant contributor to the burden of disease in women (and alcohol abuse in men). The same study reported F:M ratios of 2.3 and 1.2 for major depression (age range: 14 years and older) and bipolar disorder (age range: 18–65 years), respectively. Furthermore, in 2011, a total of 30.3 million people suffered from major depression and altogether 3.0 million from bipolar disorder in Europe (Wittchen et al., 2011). Even though there are no major gender differences in the incidence or in the clinical presentation or treatment response of bipolar I disorder, bipolar II/hypomania seems to be more common in women than in men (Di Florio & Jones, 2010). Also, there is clear evidence of an increased risk of recurrence/relapse in the postpartum period (Jones & Craddock, 2005; Di Florio et al., 2013), and women with bipolar disorder complain of menstrual irregularity and premenstrual mood worsening (Blehar et al., 1998; Rasgon et al., 2003), as well as mood lability in connection with the perimenopausal transition.

In addition to differences in the prevalence rates, differences in the onset, course and phenomenology of mood disorders also exist between men and women. With regard to major depressive disorder (MDD), women usually present with a younger age of onset, a greater risk of family history of affective disorders, and are more likely than men to experience atypical depression, sleep disturbances, psychomotor retardation, anxiety/somatic symptoms, distress (Kornstein et al., 2000a), as well as increased appetite and weight gain (Williams et al., 1995; Frank et al., 1988). Moreover, women respond to antidepressants differently compared to men, and the response depends on their reproductive stage. In fact, women usually show better response to antidepressants (especially serotonin-noradrenaline reuptake inhibitors and selective serotonin reuptake inhibitors) than men (Khan et al., 2005), and women with chronic depres-

sion, especially the young and premenopausal ones, tend to respond better and faster to selective serotonin reuptake inhibitors (sertraline) than to tryciclic antidepressants (imipramine) when compared with men. Conversely, postmenopausal women aged 40 years or older showed a similar response to imipramine and to sertraline (Kornstein et al., 2000b).

2.1.2 Anxiety disorders in women: epidemiology and phenomenology

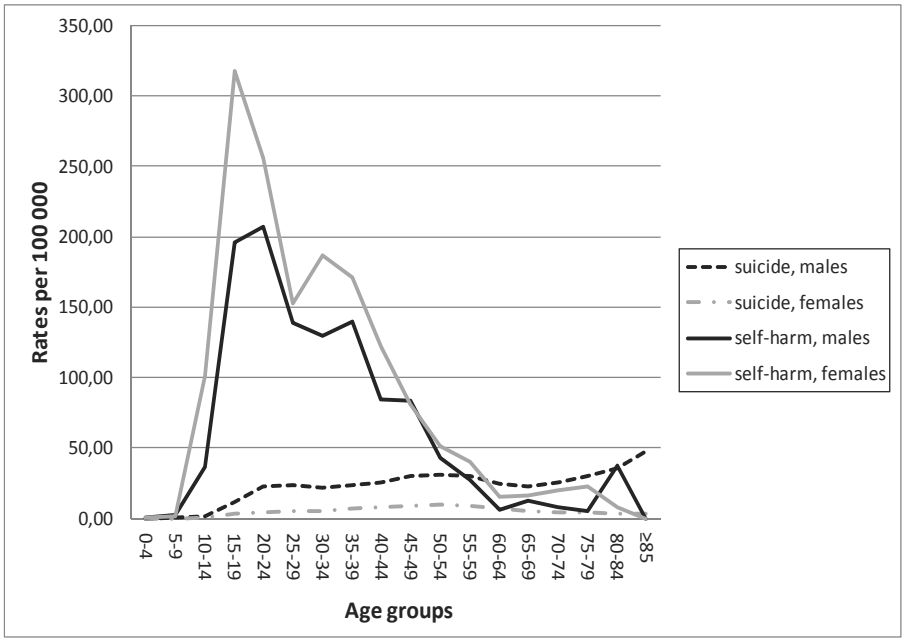
The category of anxiety disorders includes generalized anxiety disorder (GAD), social phobia, specific phobia, obsessive compulsive disorder (OCD), panic disorder (with or without agoraphobia) and post-traumatic stress disorder (PTSD). The F:M ratio of anxiety disorders as a whole is 2.5 in Europe, ranging from a 1.6 F:M ratio for OCD to a 3.1 F:M ratio for agoraphobia (Wittchen et al., 2011). Epidemiology, the clinical presentation and course of almost all anxiety disorders differs between genders. However, in general it seems that remission and relapse rates do not differ between men and women (Yonkers et al., 2003a).

In a national epidemiological survey in the USA the lifetime prevalence of GAD was 2.8% for men and 5.3% for women, with 1.2% and 2.7% 12-month prevalence rates for men and women, respectively (Vesga-López et al., 2008). Other epidemiological data showed that, compared with men, women have higher 12-month prevalence rates of GAD all throughout their life-span. For men, the highest prevalence rates are found in the age group 25–34 years (with a prevalence rate of 3.2% vs. 5.0% in women). In women, the highest GAD prevalence rates have been observed in the age group 45 years or older (prevalence rate of 6.3% vs. 0.9% in men) (Wittchen, 2002). Other studies (Yonkers et al., 2003a; Steiner et al., 2005; Simon et al., 2006) did report an earlier age at GAD onset in women than in men. Vesga-López et al.'s survey (2008) revealed several additional gender differences in the phenomenology of GAD, with men who were suffering from lifetime GAD being more likely to have a comorbid substance/alcohol use disorder and antisocial personality, and women being more likely to suffer from a comorbid anxiety (panic disorder and specific phobia) or mood (MDD, dysthymia) disorder. Men used alcohol and drugs to alleviate anxious symptoms more often than women, while women were more fatigued, had difficulties in concentration, irritability, muscle tension, as well as other associated somatic symptoms. On the contrary, women were more likely to have a family history of depression and anxiety. However, there are some inconsistencies in respect to the response to GAD treatment: indeed, while Steiner and colleagues (2005) failed to find any significant difference in the response to 12 weeks sertraline, Simon et al. (2006) reported a poorer response to fluoxetine in women (in particular among those with GAD onset in old age) than in men.

The gender differences with regard to social anxiety disorder/phobia resemble those observed in GAD (Xu et al., 2012), i.e., a F:M lifetime prevalence ratio of 1.4, comorbidity with alcohol and drug abuse, pathological gambling, conduct disorder and antisocial personality in men, and with mood and other anxiety disorders in women, and different symptoms across genders (women having worse psychosocial functioning). Several gender differences also exist with regard to OCD, in particular in respect to prevalence (higher in women than in men), age at onset (younger in men) and clinical presentation (type of onset, course of the disease and comorbidity) (Bogetto et al., 1999).

2.1.3 Suicidal behavior in women: epidemiology and phenomenology

Suicidal behavior is a complex and multifactorial phenomenon ranging from suicidal thoughts, to suicidal ideation, attempted suicide and completed suicide. In general, completed suicide is almost worldwide more common in men with a M:F ratio of 3.5:1 (WHO, 2001), while women are more likely to attempt suicide (Hawton, 2000) (Figure 1).



* USA, 2000; ** USA, 2010. Source: Centers for Disease Control and Prevention, http://www.cdc.gov/

Figure 1. Rates of self-harm injuries* and suicide in USA, by age-group and gender.**

A gender difference in the rates of completed suicide is evident already during childhood and adolescence in many countries (Gould et al., 2003; Steele & Doey, 2007; Pompili et al., 2012; Rhodes et al., 2012), with a significantly higher (3.7 times) rate of completed (but not attempted) suicide in males than in females aged 15–24 years in Europe (Värnik et al., 2009). The gender ratios in the epidemiology of completed suicide vary with regard to age. In fact, the rates of completed suicide in the USA in 1998 displayed an increase from 1.6/100 000 to 13.2/100 000, respectively, for children aged 10 to 14 years and young adults aged 20 to 24 years. Moreover, during the shift from childhood to young adulthood, there was an increase of the gender ratio (boys:girls) from 2.6:1 to 6:1 (http://www.cdc.gov/nchs/nvss/mortality/hist290.htm).

Deliberate self-harm and attempted suicides are quite rare during childhood, but their rates increase significantly during adolescence. Among children younger than 15 years, deliberate self-harm, usually impulsive and not aimed at death, is four to five times more common in girls than in boys (Hawton & Fagg, 1992; Hurry, 2000). In addition, girls are more likely to consider, plan and attempt suicide (Steele & Doey, 2007). In general, the rates of attempted suicide and suicidal thoughts are higher in female adolescents, along with higher rates of psychopathology and internalizing problems (vs. more externalizing problems in male adolescents) (Kaess et al., 2011). Lewinsohn and colleagues (2001) found an increase in the risk of attempted suicide in girls aged 13 to 18 years, with a peak between 15 and 18 years, and a slight decrease between 19 and 23 years of age. On the contrary, the risk of attempted suicide in boys increased during adolescence, with a peak at age 15 years, without reaching the female rates. In the same study the authors found that young women who had attempted suicide were more likely (than their non-suicidal counterparts) to have a history of previous suicidal ideation or attempts during adolescence, while this was not the case for young men. The authors also identified different risk factors for suicide attempt in young women and men.

The gender difference in the incidence and phenomenology of suicidal behavior persists all throughout the life span. Middle-aged women who attempt suicide are more likely to suffer from anxiety disorders, and men from alcohol and substance abuse/dependence; furthermore, middle-aged women seem to make more impulsive suicidal attempts, while men have a higher lethal intent (Monnin et al., 2012). Gender differences also exist with respect to repetition of suicidal attempts, while male repeaters are more likely to suffer from substance use disorders, and female repeaters from PTSD (Monnin et al., 2012).

Men and women appear to display different patterns of attitudes and beliefs against suicide ("reasons for living"), with young and middle-aged women reporting significantly higher scores on the reason-for-living scale in general, as well as for specific items (in detail: "fear of suicide", "survival and coping beliefs", "child-related concerns", "moral objections" and "responsibility to family") than men (Dobrov et al., 2004; Pompili et al., 2007). Additionally, increasing age was found to be associat-

ed with higher levels of responsibility to family, fear of suicide and fear of social disapproval in men but not in women (McLaren, 2011).

Table 1. Gender differences in psychiatric disorders.

	Overall 12-month prevalence (general population)	F:M ratio	Source	Phenomenology: F vs. M
MDD	6.9%	2.3	Wittchen et al., 2011*	• younger age at onset • family history of affective disorders • atypical depression • sleep disturbances, psychomotor retardation, anxiety/somatic symptoms, distress, increased appetite and weight gain
Bipolar disorder	0.9%	1.2	Wittchen et al., 2011	---
Panic disorder	1.8%	2.5	Wittchen et al., 2011	• older age at onset • risk of agoraphobia and other avoidance behaviors • comorbid anxiety disorders • longer duration of illness
Agoraphobia	2.0%	3.1	Wittchen et al., 2011	---
Social phobia	2.3%	2.0	Wittchen et al., 2011	• comorbid mood and other anxiety disorders • worse psychosocial functioning
GAD	1.7–3.4%	2.1	Wittchen et al., 2011	• younger age at onset • comorbid anxiety or mood disorders • fatigue, difficulties in concentra-- tion, irritability, muscle tension
Specific phobias	6.4%	2.4	Wittchen et al., 2011	---
OCD	0.7%	1.6	Wittchen et al., 2011	• older age at onset • clinical presentation (type of onset, course of the disease and comorbidity) • aggressive and contamination obsessions and cleaning rituals
PTSD	1.1–2.9%	3.4	Wittchen et al., 2011	• longer persistence of symptoms
Suicidal ideation	3.7%	1.2	Crosby et al., 2011**	• more "reasons for living"
Attempted suicide	0.5%	1.4	Crosby et al., 2011	• comorbid anxiety disorders (vs. alcohol and substance abuse/ dependence in men) • impulsive suicidal attempts
Completed suicide	0.01%	0.6	WHO, 2008***	---

* catchment area: Europe; study design: systematic literature review + re-analyses of existing datasets.
** catchment area: USA; study design: national survey.
*** catchment area: all countries.
Abbreviations: Generalized Anxiety Disorder (GAD); Major Depressive Disorder (MDD); Obses-sive-Compulsive Disorder (OCD); Post-Traumatic Stress Disorder (PTSD).

In general, it is not possible to rule out that the above described results from the literature review are partly affected by a report bias, with women being more prone to report and seek clinical help for depressive (especially somatic [Silverstein, 1999]) and anxiety symptoms. However, taken together these findings suggest that men and women differ with regard to their vulnerability to psychiatric symptoms and disorders, including risk behaviors. In detail, it seems that the gender differences are not merely epidemiological, but also clinically evident in terms of temporal course and manifestations of diseases.

2.2 Psychopathology in women's reproductive life

2.2.1 Premenstrual Syndrome and Premenstrual Dysphoric Disorder

The Premenstrual Syndrome (PMS) is a general complex of severe, recurrent symptoms temporally related with the menstrual phase (Johnson, 1987). By definition, these symptoms occur seven to ten days before menses and end with their onset. Common symptoms of the PMS include anxiety, irritability, nervousness (sometimes leading to behavior detrimental to self, family and society), water and salt retention, abdominal bloating, mastalgia, craving for sweets, increased appetite, weight gain, palpitation, fatigue, headache and the shakes. A less common but most severe syndrome is associated with depressive symptoms, insomnia, confusion and increased risk of suicide (Abraham, 1983). Although the majority of women worldwide do present with some kind of premenstrual symptoms, around 13% to 18% of women of reproductive age have symptoms severe enough to be classified as PMS (Halbreich et al., 2002). The onset is usually with the menarche and in adolescence the symptoms frequently interfere with daily activities (Cleckner-Smith et al., 1998).

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) defines the Premenstrual Dysphoric Disorder (PMDD) as a "depressive disorder not otherwise specified", characterized by "physical symptoms associated with depressed mood or dysphoria, affective lability, decreased interest in usual activities, concentration difficulties, and others; symptoms are present for most of the time during the last week of the luteal phase, begin to remit within a few days after the onset of the follicular phase, and are absent in the week postmenses". The estimated prevalence of PMDD ranges between 1% and 7% (Halbreich et al., 2002; Wittchen et al., 2002; Halbreich et al., 2003; Hong et al., 2012; Pilver et al., 2013).

There is a reciprocal association between PMS/PMDD and depressive/anxiety disorders: indeed, women with premenstrual dysphoric patterns are at increased risk for previous and subsequent episodes of MDD. A higher than 20% comorbidity rate

was found between PMDD and other mood disorders (Wittchen et al., 2002; Forrester-Knauss et al., 2011), and a 44.7% comorbidity rate with anxiety disorders (Wittchen et al., 2002). On the other hand, women suffering from PMS/PMDD are more likely to have a history of past MDD (Critchlow et al., 2001). The premenstrual period *per se* seems to be a risk for the exacerbation of pre-existent psychiatric symptoms or disorders (Endicott & Halbreich, 1988), such as more prominent alcohol use in the case of alcoholism, symptom increase in the case of schizophrenia, or even higher rates of suicide attempts (Keye et al., 1986; Stout et al., 1986). In fact, women suffering from PMS/PMDD have an elevated risk of suicidal, aggressive or impulsive behavior (Endicott & Halbreich, 1988; Wittchen et al., 2002), and 24% of women with PMDD reported suicidal thoughts (Yonkers et al., 2003b).

2.2.2 Perinatal disorders

MDD during pregnancy is characterized by the same features than in other phases of women's lives (American Psychiatric Association, 2000). It seems that around 18.4% of pregnant women experience depressive symptoms, and 12.7% suffer from a major depressive episode (MDE) (Gavin et al., 2005) during pregnancy. Gotlib and colleagues (1989) found 25% of 360 pregnant women reporting depressive symptoms, and 10% suffering from MDD. Similarly, a 12.4% prevalence and a 2.2% incidence rate of depressive disorder (either minor or major) were detected during pregnancy in a recent longitudinal study (Banti et al., 2011). Marcus and colleagues (2003) reported a 20.4% rate of depressive symptoms among pregnant women screened in an obstetric setting, and Evans et al. (2001) found in their cohort study more depressive symptoms during pregnancy than after the delivery itself, in line with the results reported by Banti et al. (2011). However, it is likely that the real prevalence of MDD during pregnancy is underestimated due to misunderstanding of the symptoms (e.g. insomnia and altered appetite, thought to be normal reaction to pregnancy) and due to the stigma associated with mental illness.

Potential risk factors for depressive symptoms during pregnancy include substance and alcohol misuse and cigarette smoking during pregnancy, self-rated poor general health, being unmarried/without a partner, unemployed and having a lower education level (Marcus et al., 2003), having a family or personal past history of depression, negative life events, lack of social (and partner) support, domestic violence and unintended pregnancy (Lancaster et al., 2010).

Anxiety disorders in general are quite common during pregnancy (Ross & McLean, 2006). In a survey on anxiety disorders and depression in the perinatal period, Sutter-Dallay and colleagues (2004) found 24% of participants suffered from anxiety disorders, and 5.7% from MDD during pregnancy, with a significant proportion of comorbidity. Indeed, women suffering from anxiety disorders during pregnancy seem to be at elevated risk of developing depressive symptoms and/or disorders in the per-

inatal period (Sutter-Dallay et al., 2004; Banti et al., 2011), and women suffering from depressive symptoms during pregnancy are at increased risk of developing postpartum depression (in Lee & Chung, 2007).

Between 30% and 75% of live births are followed by post-partum blues, i.e. mild depressive symptoms with onset three to four days after delivery and lasting less than two weeks (O'Hara et al., 1990). Women who experience post-partum blues may themselves be at risk of developing depressive disorder during the first post-partum year (Bloch et al., 2005). Post-partum depression is characterized by symptoms of an MDE, but with onset within four weeks of delivery (American Psychiatric Association, 2000). It may last up to six months post-partum or even longer. In general, it seems that the prevalence of depression during pregnancy or in the post-partum is rather similar to that in the general population, even if different rates are reported in the literature due to different diagnostic methods, different study designs (retrospective or prospective), and whether the studies distinguish between MDD in the post-partum and post-partum-onset depression (Gavin et al., 2005).

A systematic review (Gavin et al., 2005) reported a 19.2% prevalence of major or minor depression during the first 3 months postpartum, and Banti and colleagues (2011) reported a 9.6% prevalence rate of depressive disorder (either minor or major) in the 1-year postpartum, with an incidence rate of 6.8%. O'Hara and Swain (1996) found an average prevalence of post-partum depression in the general population of 13%, and Georgiopoulos et al. (1999) found an 11.5% rate of depressive symptoms in a sample of 909 women assessed at week 6 post-partum; 5.3% had suicidal ideation in the previous week (1.4%) or infrequent thoughts of self-harm (3.9%).

Possible risk factors for post-partum depression include past history, as well as family history of psychological disorders; psychological disorders during pregnancy; previous postpartum depression; poor marital relationship; lack of social and spousal support (Seyfried & Marcus, 2003), as well as premenstrual irritability and/or mood changes (Sugawara et al., 1997). Possible protective factors include being breastfeeding and living with a spouse or a significant other (Yonkers et al., 2001).

The perinatal period is also an at-risk-period for other psychiatric illness, often associated with discontinuation of the pharmacological treatment. A severe post-partum psychosis occurs in around 0.05% to 0.2% of new mothers, especially in women with a previous diagnosis of bipolar disorder (Gitlin & Pasnau, 1989; Jones & Craddock, 2001; Di Florio et al., 2013); its onset is usually within four weeks after delivery.

2.2.3 Perimenopausal disorders

Menopausal transition is known to be a sensitive period in a woman's life, partly due to its broad psychological and social correlates and partly due to the considerable hormonal changes that it implies.

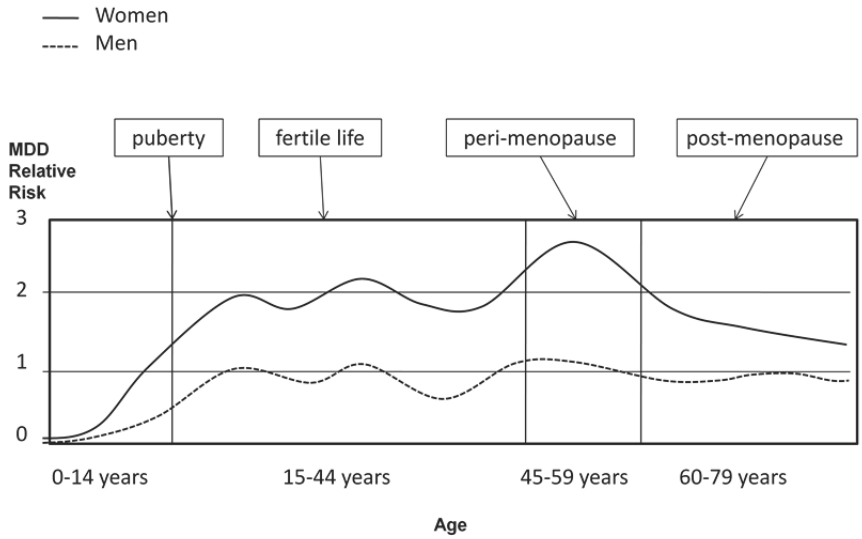
Even though the female predominance in the prevalence of depressive disorder seems to be slightly less evident after menopause (Weissman & Olfson, 1995), and the majority of women do not develop depressive symptoms or disorders in connection with the menopausal transition, nevertheless a subgroup of women seem to be more vulnerable to mood impairment during the perimenopause. Albeit some inconsistencies (Vesco et al., 2007), studies report an increased risk (OR 1.8 to 2.9) of depressive symptoms (low mood, irritability and difficult concentration) and disorders in the perimenopause when compared with the premenopause (Freeman et al., 2004; Freeman et al., 2006), even in women with no history of past depressive disorder (Cohen et al., 2006). Specifically, the risk of depressive symptoms/disorders is high either in the early stages of the perimenopausal transition, i.e. when the estrogen levels are transiently high (Freeman et al., 2004; Freeman et al., 2006), or during the late stage, i.e. when the estrogen withdrawal is more significant (Schmidt et al., 2004; Steinberg et al., 2008). Additionally, recent results from the SWAN study (Study of Women's Health Across the Nation) (Bromberger et al., 2011) show that the risk of suffering from an MDE is higher during the menopausal transition as well as in the short term (within 2 years) after entering the menopause, than premenopausally.

Taken together, these findings support the hypothesis of a hormonal contribution, in particular of hormone (especially estrogen) variability rather than increase or decrease (Freeman et al., 2006), to the psychological distress typical of this reproductive phase (Harsh et al., 2009). Other risk factors for perimenopausal depression include young age at menarche, heavy and irregular menstrual bleeding during the first five years of menstruation, a past history of depression (Hay et al., 1994), premenstrual dysphoria (Steinberg et al., 2008) and stressful life events in connection with the menopausal transition (Cohen et al., 2006). Reciprocally, women with a past history of MDD, especially those with more severe depressive symptoms, are at higher risk of an early decline in ovarian function and therefore of early transition to perimenopause when compared with women with no history of depression (Harlow et al., 2003).

With regard to the prevalence of anxiety symptoms during the menopausal transition, the data are quite inconsistent and inadequate (Bryant et al., 2012). A study (Seritan et al., 2010) found no difference between pre-, peri- and post- menopausal women participating in an assessment program for midlife women, even though perimenopausal women were more likely to report depressive/anxiety symptoms than the postmenopausal ones. In a study carried out among peri- and postmenopausal women in a clinical setting, a 48.6% prevalence rate of anxiety was found (Terauchi et al., 2012), and 23.8% of postmenopausal women attending a gynecologic outpatient clinic had a diagnosis of anxiety disorder, the most common one being GAD (15.6%) (Sa-

hingoz et al., 2011). Moreover, the presence of anxiety/depressive symptoms was associated with the severity of vasomotor symptoms in peri- and postmenopausal women (Seritan et al., 2010).

The prevalence rates of mood and anxiety symptoms and disorders through women's reproductive lives are summarized in Table 2. Figure 2 displays the gender difference in the relative risk of MMD across the life-span.



Abbreviations: Major Depressive Disorder (MDD).

Figure 2. Risk of depression across the (female) reproductive life span: gender differences (adapted from Deecher et al., 2008).

Table 2. Mood and anxiety disorders through women's reproductive lives.

	Menstrual cycle			Pregnancy			Postaprtum			Perimenopause-menopause		
	symptoms	prevalence	source	symptoms	prevalence	source	symptoms	prevalence	source	symptoms	prevalence	source
Depressive symptoms or disorders	PMS	13–18% (women of repro-ductive age)	• Halbreich et al., 2002	depressive symptoms	18.4–25% (pregnant women)	• Gotlib et al., 1989 • Marcus et al., 2003 • Gavin et al., 2005	postpartum blues	30–75% (postpartum women)	• O'Hara et al., 1990	depressive symptoms	15–50% (perimeno-pausal women)	• Clayton et al., 2008 • Timur & Sahin, 2010
	PMDD	1–7% (women of reproductive age)	• Halbreich et al., 2002 • Wittchen et al., 2002 • Hong et al., 2012 • Pilver et al., 2013	MDE	12.7% (pregnant women)	• Gavin et al., 2005	major or minor depression (3 months postpartum)	19.2% (post-partum women)	• Gavin et al., 2005			
				major or minor depression	10–12.4% (pregnant women)	• Gotlib et al., 1989 • Banti et al., 2011	major or minor depression (1-year postpartum)	9.6% (post-partum women)	• Banti et al., 2011			
Bipolar disorders	menstrual irregularity, premenstrual mood change	65–67% (bipolar women)	• Blehar et al., 1998 • Rasgon et al., 2003	symptom worsening	50% (bipolar parous women)	• Freeman et al., 2002	associated postpartum psychosis	50% (bipolar parous women)	• Jones & Craddock, 2001	mood lability, depressive symptoms	20–68% (bipolar women)	• Blehar et al., 1998 • Freeman et al., 2002 • Marsh et al., 2008
							first or recurrent postpartum episodes	25–67% (bipolar parous women)	• Hunt & Silverstone, 1995 • Freeman et al., 2002			
Anxiety symptoms or disorders	premenstrual anxious symptoms	1–10% (13-18 year old girls)	• Cleckner-Smith et al., 1998	OCD	0.2–1.2% (pregnant women)	• Ross & McLean, 2006	OCD	2.7–3.9% (postpartum women)	• Ross & McLean2006	OCD	7.1% (post-menopausal, clinical setting)	• Uguz et al., 2010
				anxiety disorders during pregnancy	24% (pregnant women)	• Sutter-Dallay et al., 2004	GAD	4.4–8.2% (8-week postpartum women)	• Wenzel et al., 2003 • Wenzel et al., 2005	GAD	15.6% (post-menopausal, clinical setting)	• Sahingoz et al., 2011
							panic disorder	1.4% (8-week postpartum women)	• Wenzel et al., 2005	anxiety symptoms or disorders	48.6% (peri- and post-menopausal, clinical setting)	• Terauchi et al., 2012
										any anxiety disorder	23.8% (post-menopausal, clinical setting)	• Sahingoz et al., 2011

Abbreviations: Generalized Anxiety Disorder (GAD); Major Depressive Episode (MDE); Obsessive-Compulsive Disorder (OCD); Premenstrual Dysphoric Disorder (PMDD); Premenstrual Syndrome (PMS).

2.2.4 Suicidal behavior through women's reproductive life

Suicidal behavior and menstrual cycle phase. Research focusing on the associations between suicidal behavior and reproductive life in women has produced quite mixed findings (Table 3), with studies reporting no relationships (Helweg-Larsen & Hestbech, 1985; Vanezis, 1990; Mann et al., 1999), and others supporting the association between completed suicide and menstrual cycle phase. However, even among the latter group, there are many inconsistencies. Indeed, Targum et al. (1991) and Gisselmann et al. (1996) reported that suicide occurs more frequently in the pre-ovulatory or paramenstrual phase, while McKinon and colleagues (1959) found an association between suicide (and accidental death) and luteal phase, with a peak in the mid-luteal phase. Other authors (in: Saunders & Hawton, 2006; Dogra et al., 2007) showed a relationship with the late luteal/early follicular phase (menstrual bleeding), with 15% to 100% of women committing suicide while menstruating. Similarly, Fourestié et al. (1986) and Caykoylu et al. (2004) suggested an higher suicide risk in the menstrual follicular phase, while a more recent histopathological study found a significant association between suicide and menstrual phase when comparing 56 women who died by suicide with a control group of 44 women who died due to other causes (25% vs. 4.5%) (Leenars et al., 2009). Several studies also found that suicidal thoughts are more common when estrogen levels are low, i.e. in the premenstrual and menstrual phases (Mandell & Mandell, 1967; Wetzel et al., 1971; Chaturvedi et al., 1995).

Although a clear consensus does not exist in respect to attempted suicide (Holding & Minkoff, 1973; Birtchnell & Floyd, 1974; Luggin et al., 1984; Ekeberg et al., 1986; Gisselmann et al., 1996), it seems justified to state that an association with the menstrual and premenstrual phases does exist. Indeed, Dalton (1959) reported a higher number of attempted suicides during the early menstrual and premenstrual phases, and Tonks and colleagues (1968) detected a slightly higher prevalence of attempted suicide during the menstrual and luteal phases. Fourestié and colleagues (1986) found that the highest number of suicide attempts in women who did not use oral contraception occurred during the first (42%) and after the fourth (12%) week of the menstrual cycle, i.e. in low-estradiol phases. This is consistent with Baca-Garcia and co-authors (1998), who found a high incidence of suicide attempts in the first (36%) and in the fourth (29%) week of the menstrual cycle, and a significantly higher than expected number of suicide attempts during the follicular (especially menstrual) phase (Baca-Garcia et al., 2000). In their replication study Baca-Garcia et al. (2003a) again showed that suicide attempts tend to be associated with the menses. Using the combined results of their studies, the authors stated that "the probability of attempting suicide during the menses was 1.68 times higher than the overall probability of attempting suicide for any fertile women".

Furthermore, the risk of suicidal, aggressive or impulsive behavior is higher in women with PMS/PMDD (Endicott & Halbreich, 1988), and the rates of suicidal ideation among women contacting a clinic for PMS ranged from 17% to 63% (Halbreich et al., 1982; Stout et al., 1986). Recent data from a national representative sample of American women (Pilver et al., 2013) found a gradual rise in the prevalence of suicidal behavior (ideation, plans and attempts) from women with no premenstrual symptoms, to women with moderate/severe PMS, to women with PMDD. In the same study, moderate/severe PMS was associated with risk of suicidal ideation (OR 1.49), and PMDD with an increased risk of suicidal ideation (OR 2.22), suicidal plans (OR 2.27) and attempts (OR 2.10). Similar results were gained from a Korean study, where women with PMDD had a higher risk of lifetime and 12-month suicidal ideation compared with women with no PMDD (similar, but non-significant trends were detected in respect to suicidal plans and attempts) (Hong et al., 2012). Reciprocally, women with suicidal ideation are more likely to complain of premenstrual symptoms such as low mood, irritability and water retention (Chaturvedi et al., 1995).

Table 3. Suicidal behavior during the menstrual cycle.

	Menstrual cycle phase			
	No relationship	**Pre-ovulatory or para-menstrual phase**	**Late-luteal or men-strual-follicular phase**	**Mid-luteal phase**
Completed suicide	Helweg-Larsen & Hestbech, 1985 Vanezis, 1990 Mann et al., 1999	Targum et al., 1991 Gisselmann et al., 1996	Fourestié et al., 1986 Caykoylu et al., 2004 Saunders & Hawton, 2006 Dogra et al., 2007 Leenaars et al., 2009	McKinon et al., 1959
Attempted suicide	Holding & Minkoff, 1973 Birtchnell & Floyd, 1974 Luggin et al., 1984 Ekeberg et al., 1986 Targum et al., 1991	---	Dalton, 1959 Tonks et al., 1968 Fourestié et al., 1986 Baca-Garcia et al., 1998 Baca-Garcia et al., 2000 Baca-Garcia et al., 2003a	---
Suicidal ideation	---	---	Mandell & Mandell, 1967 Wetzel et al., 1971	---

Suicidal behavior and pregnancy. Although the rates of attempted and completed suicide are quite low during pregnancy and in the postpartum (Appleby, 1991; Syverson et al., 1991; Appleby, 1996; Marzuk et al., 1997; Catalan, 2000), high levels of suicidal ideation (16.7% to 27.8%) were found among pregnant women (Newport et al., 2007), especially in the cases of unplanned pregnancies, depressed, anxious, unmarried and less-educated women (Newport et al., 2007). The authors suggested that hormonal changes during pregnancy may influence suicide ideation. However, it is possible that the psychosocial "supportive" milieu typical of pregnancy and postpartum may contribute reducing the risk of acting on suicidal thoughts (Newport et al., 2007).

Also, it seems that the pregnancy outcome itself may influence the suicidal risk in the postpartum period, with higher suicide rates in women who had a miscarriage (18.1/100 000 miscarriages) or an induced abortion (34.7/100 000 abortions) than in the cases of live births (5.9/100 000 live births) (Gissler et al., 1996). Similarly, Reardon et al. (2002) found that in the eight years after the first pregnancy event, women with induced abortion as the outcome were 62% more likely to die (from non-violent causes, suicide and accidents) than women who gave birth and had no history of induced abortion. This is consistent with other findings showing a (bidirectional) association between induced abortion and suicidal behavior (Morgan et al., 1997; Mota et al., 2010).

Suicidal behavior and menopause. Ultimately, there is a general lack of information on the relationship between completed suicide and menopause. However, Baca-Garcia and colleagues (2010) reported that women who attempted suicide during low-estrogen and low-progesterone states (as it is in menopause) presented more severe lethal intent than women who attempted suicide in other states, and Usall and colleagues (2009) found higher risk of suicidal ideation in perimenopause than in pre- or post-menopause, independently of any comorbid mood or anxiety disorder.

In conclusion, it seems that a relationship does exist between mental health and reproductive life in women. It is worth remembering that "reproductive life" is a complex entity with a broad range of physical and psychological correlates. Indeed, reproductive events are characterized by significant changes in hormone levels as well as by macroscopic changes in the body and in its functions. Moreover, reproductive events cannot be separated by their psychological and social correlates, being generally associated with important role transitions. It is thereby understandable how reproductive life may have an impact on women's mental health, or more generally, psychological well-being. In addition, it is clear how complex this relationship is, and how difficult it is to clearly disentangle the role of the biological from that of psychological factors.

2.3 Gender differences and associated factors in affective disorders and suicidal behavior

There are many possible explanations for the gender difference in the epidemiology and phenomenology of many psychiatric conditions, including suicidal behavior. Indeed, psychiatric disorders and suicidal behavior are complex entities, with a multifactorial etiology that includes cultural, social and biological aspects.

2.3.1 Cultural and social factors

Several cultural and social factors may contribute to the greater risk of depression and anxiety in women and to the higher risk of completed suicide in men (and attempted suicide in women).

Sociodemographic factors. Among other sociodemographic factors, marital status and social integration seem to play a role. Even though with mixed findings, marriage has been claimed as protective, or beneficial, for the mental health of men more than women (Wu & DeMaris, 1996; Kiecolt-Glaser & Newton, 2001), possibly due to women's higher proneness to experiencing lower marital satisfaction, more marital distress and worse marital quality than men (Schumm et al., 1998). Specifically, recently it has been shown (Scott et al., 2010) that marriage is associated with a reduced risk of mental disorders in general in men as well as in women engaged in their first marriage when compared with never married individuals. However, when looking at the single diagnoses separately, the reduction in the risk of MDD, dysthymia and panic disorder was evident only for men; on the contrary, a reduced risk for substance abuse was more prominent in women. Different effects of marriage in respect to gender where found also in an elderly population, where marriage *per se* (i.e., even in the presence of marital conflicts) was protective against depression in men, but not in women (Mechakra-Tahiri et al., 2010). Moreover, the end of a relationship (due to separation, divorce – even in the case of a remarriage – or widowhood) seems to be associated with an increased risk of any mental disorder both in men and women (when compared with currently married subjects), but again the associations were more evident among men as regards depressive disorders, and in women in respect to substance abuse (Scott et al., 2010). However, married women with a diagnosis of bipolar disorder were found to have less depressive episodes and less severe depressive scores when compared with unmarried bipolar women, while no difference was found between married and unmarried bipolar men (Lieberman et al., 2010).

Cultural factors. Cultural factors may also partly explain the so-called "gender paradox" in suicide (Canetto & Sakinofsky, 1998). A less perceived need for help and lower access to the health care systems, as well as higher levels of impulsivity and aggressiveness in men may contribute to the higher suicide rates in men compared with women. Women more frequently choose less lethal suicidal methods such as drowning and poisoning (overdoses). On the other hand, men tend to choose more aggressive methods which often result in completed suicide (Rich et al., 1988; Marusic, 1999). However, the choice of suicide methods is not an exact measure of the real lethal intent, but it can rather be an expression of a cultural influence in the choice of the suicidal means, with poisoning by psychotropic drugs being a typical "feminine" method of suicide (Canetto & Sakinofsky, 1998). Indeed, in western countries, such as the United States, suicide is usually viewed as a "masculine" behavior, and therefore inappropriate for women, while attempted suicide is considered more "feminine" behavior (Canetto, 2008). Additionally, masculinity, in contrast to femininity, often means strength, decisiveness and inexpressiveness of emotions; hence, an inability to fulfill this role, along with the impossibility of expressing emotions, may lead to risky behaviors (Canetto & Cleary, 2012). In other cultures, including China, suicide is considered an act of the powerless, and men who commit suicide are considered weak and effeminate (Canetto, 2008). In this context suicide is usually in response to interpersonal conflicts/abuse within the family, and is considered a socially acceptable means of revenge for the powerless, as women usually are within these societies. These social and cultural beliefs certainly do play a role in determining the typical epidemiological pattern of suicidal behavior (Canetto, 2008).

Another hypothesis is that the gender difference in psychiatric disorders reflects a difference in the "gender roles", which includes different life events and stressors, along with different coping skills, among men and women in the context of their countries and cultures. As a consequence of this theory, the increasing equality between men and women in many countries has been accompanied by a progressive reduction in the gender gap in depression and other disorders. Recently, it has been shown (Seedat et al., 2009) that the gender difference in the prevalence of MDD and substance abuse is smaller (i.e., there is a trend for less depressed, but more abuser women) in the younger than in the older generations. This phenomenon was accompanied by a progressive reduction in the gender role traditionality (in terms of women's education and employment, age at marriage and use of contraception), suggesting that the closer the gender roles come together, the smaller the differences in the epidemiology of "gender-related" phenomena, such as the prevalence of some psychiatric conditions (including suicidal behavior).

2.3.2 Biological factors

Along with cultural and social background, biology has to be taken into account when looking at psychiatric disorders and at their epidemiology. Male and female brains significantly differ at structural, neurochemical and molecular levels. Several factors such as hormone-independent, genetic (Arnold et al., 2003) and environmental agents intervene in determining the sexual differentiation of the brain, which starts already during the fetal life. Additionally, sexual hormones are known to primarily contribute to this process. These and other biological differences could partly explain the pattern of the epidemiology of many mental disorders, such as depression.

2.3.2.1 Structural brain differences

In addition to the microscopic structural differences (cell size, characteristics and number of axons, dendrites and spines), there are several macroscopic gender differences in the brain. The overall volume of the male brain is larger than the volume of the female brain (though women have greater cortical thickness than men), with the amygdala and cerebellum being larger in men and the hippocampus in women, and women having a higher percentage of gray matter relative to the total intracranial volume (Gur et al., 1999; in Cosgrove et al., 2007). Also the nucleus of the preoptic area in the hypothalamus is larger and contains more cells in men than in women. Other brain structures related to emotions differ between men and women, with the cingulated and the ventrolateral prefrontal cortices being larger in women. Paus and coworkers (2010) found that the overall brain volume, as well as the absolute volumes of the white and, to a lesser extent, the gray matter, are already higher in male than in female adolescents. However, the gray matter volume corrected for the total brain volume was higher in girls than in boys, and the opposite with regards to the white matter. Also, they found that the (absolute and relative) volume of white matter increases with age significantly more in male than in female adolescents, while relative gray matter volume decreases with age similarly in adolescent boys and girls. It has also been shown that the volume of the gray matter in some cerebral regions may vary during the menstrual cycle (declining during ovulation), and is larger in women using hormonal contraception (Pletzer et al., 2010). Moreover, the global cerebral blood flow is higher in women than in men, and an estrogen-dependent regulation has been hypothesized (Cosgrove et al., 2007).

2.3.2.2 Genetic influence

Genetic factors play a role in the complex, multifactorial etiology of depression, and several genes and gene polymorphisms, especially those involving components of the monoaminergic systems (e.g., catechol-O-methyltransferase, monoamine oxidase A, serotonin transporter), have been suggested as potential candidates. Additionally, many studies have provided evidence for gender differences in the genetic susceptibil-

ity to depression, and a genome-wide association study revealed several gene–gender interactions, as well as gender-specific gene associations, in relation to MDD (Aragam et al., 2011). It is therefore possible that, due to different gene expressions, steroid hormones have different effects in female and male brain.

Specifically, the activity of the catechol-O-methyltransferase is less pronounced in women than in men (due to an estrogen-mediated down-regulation), and the specific polymorphisms of the catechol-O-methyltransferase gene associate with psychiatric disorders and poor response to antidepressants in men but not in women (Tsai et al., 2009). Furthermore, the association between depression and stress, as well as the serotonin turnover itself, vary between genders according to different polymorphisms of the serotonin transporter gene (Williams et al., 2003; Brummett et al., 2008; Hammen et al., 2010).

Several other genes seem to be involved in the gender difference of MDD (e.g., the protein tyrosine phosphatase receptor R gene, an androgen-regulated gene whose expression varies with menstrual cycle phase) (Shi et al., 2012). Also, a rare allelic variant of the gene encoding for preprogalanin (a precursor of the amino acid peptide galanin) was found to be associated with more severe anxious symptoms in female, but not male, patients, and with more severe depressive symptoms (and less likelihood of remission) in female premenopausal, but not postmenopausal or male patients (Unschuld et al., 2010).

Taken together, these findings, along with many other reports on a gene–gender interaction in relation to depression and other psychiatric disorders, contribute to explaining the gender difference in the epidemiology, onset and course of depression, anxiety and other psychiatric disorders.

2.3.2.3 Immune systems

The importance of the immune system in depression, anxiety and several other psychiatric disorders has been highlighted over the past 20 years (Maes, 2011). Specifically, depression is characterized by markers of inflammatory response (e.g., increased levels of interleukin-1β, interleukin 6 and tumor-necrosis factor-α). In particular, depression seems to be associated with a cell-mediated immune activation, with a Th1/Th2 balance shifted towards Th1 and increased levels of serum interleukin 2 receptor concentrations. These alterations are linked to the altered glucocorticoid response and to the tryptophan depletion typically found in depressed patients (Maes, 2011).

In general, the immune response differs by gender especially during fertile life. Several components of the immune systems, including B and T lymphocytes, neutrophils and macrophages express (nuclear and membrane) estrogen receptors. Furthermore, estrogens are known to modulate the maturation of B and T cells, high levels of estrogens being associated with a Th1/Th2 ratio in favor of Th2, and low estrogen levels (as it is the case during the menstrual and luteal phases) with a balance shifted towards Th1. Additionally, estrogens have a promoting effect on B-lymphocytes, while

the levels of neutrophils have been found to vary according to the menstrual cycle phase (Pennell et al., 2012).

This evidence supports the hypothesis of an interaction between gonadal hormones and the immune system, and its possible contributive role in the gender difference in depression and other psychiatric disorders.

2.3.2.4 Neurotransmitters

According to the so-called "monoaminergic theory", depression arises from altered levels of neurotransmitters, such as serotonin, noradrenalin and dopamine. Gender differences in the levels, synthesis and/or metabolism of these peptides, as well as in the localization and function of the monoaminergic, cholinergic, GABAergic and peptidergic systems, may partly explain the gender difference in many psychiatric disorders.

Serotonin. In general, women have higher blood serotonin and lower plasma levels of 5-hydroxyindoleacetic acid than men (Ortiz et al., 1988). However, serotonin synthesis was found (Nishizawa et al., 1997; Sakai et al., 2006) to be much (52%) lower in several brain regions in healthy women than in men, even though the amount of serotonin stored in the brain is probably similar between genders. The gender difference in the synthesis of serotonin is more evident in the left side of the brain and it only involves the cortical regions (Sakai et al., 2006). Nishizawa and colleagues (1997) hypothesized that a higher use than usual of serotonin in response to stress is accompanied in women (but not in men) by reduced, or not effective enough, serotonin synthesis, this in turn resulting in serotonin depletion that could explain the proneness to stress-triggered depression in women. Also, in the same study the authors found that acute tryptophan depletion led to a significantly larger reduction of serotonin synthesis in women than in men. However, other studies found that the serotonin synthesis was higher in several cortical regions, as well as in some regions of the limbic system, in women with a diagnosis of MDD than in men suffering from MDD (Frey et al., 2010).

Regarding the serotonin receptor and transporter, the serotonin receptor 5-HT1A binding potential is (39%) higher in healthy women than in men (Jovanovic et al., 2008), and it was found to decrease with age in men but not in women (Cidis Meltzer et al., 2001). On the contrary, men exhibit a (55%) higher serotonin transporter binding potential than women (Jovanovic et al., 2008), even though its density in the diencephalon seems to be lower in depressed (young) women compared with healthy controls and depressed men. Interestingly, the number of diencephalon serotonin transporters decreased with age in healthy women and men as well as in depressed men, but increased in depressed women (Staley et al., 2006).

These findings suggest that baseline serotonin activity is higher in women than in men, but a gender-specific (probably estrogen-mediated) modulation of the serotoninergic activity in women may lead to enhanced vulnerability to depression.

Dopamine, Noradrenalin and Gamma-Aminobutyric Acid. Dopamine activity and dopamine transporter levels are higher in women than in men; this probably explains, at least in part, the higher rates of alcoholism and related disorders in men than in women (Cosgrove et al., 2007). Cortical gamma-aminobutyric acid levels are also higher in women than in men, and they seem to change accordingly to the menstrual cycle phase (high in the follicular, low in the luteal phase in healthy women, and vice versa in women with PMS) (Epperson et al., 2002).

There is scant information on the gender difference in cerebral noradrenalin, in spite of its well-established role in depression. However, levels of noradrenalin were found to correlate with the severity of alexithymia in depressed men but not women (Spitzer et al., 2005). Moreover, it seems that the levels of a noradrenalin metabolite, the 3-methoxy-4-hydroxyphenylglycol, vary with age to out-range (either below or above the physiological range) values in women but not in men, thus suggesting a dysregulation of the noradrenergic system that could possibly partly explain the vulnerability to depression in women (Halbreich & Lumley, 1993).

2.3.2.5 Hormonal influence

Many hormonal systems are known to contribute to the etiology of depression and other psychiatric disorders. The most widely studied ones are the thyroid hormones, cortisol, estrogens and progesterone and, more recently, melatonin. It is plausible that these hormonal systems and their brain actions exhibit a gender pattern that could explain gender differences in psychiatric disorders.

Thyroid hormones. Thyroid diseases are significantly more frequent in women than in men (Vanderpump et al., 1995). Impaired thyroid function is related with depressive and anxiety symptoms and disorders, and thyroid hormones are considered to interact with neurotransmitter systems (such as the serotoninergic and dopaminergic systems) known to be involved in the etiology of mood disorders (Bauer et al., 2002; Bauer et al., 2008). Reciprocally, even though overt hypo- or hyper- thyroidism are rare among depressed outpatients, a proportion of them do exhibit a trend for subclinically altered levels of thyroid hormones (Fava et al., 1995; Bauer et al., 2008).

In general, although the connection between the high prevalences of thyroid diseases and depression and other psychiatric disorders in women is unclear, it is not possible to rule out its contributive role to women's high vulnerability to depression.

Cortisol. Abnormal cortisol levels are associated with depression, with a proportion of depressed patients exhibiting higher mean cortisol levels and no cortisol decrease in response to a dexamethasone suppression test both in men and women. However, some gender differences in cortisol secretion, levels and activity have been detected. The hypothalamic regions responsible for the secretion of the corticotropin-releasing hormone present a sexual dimorphism, with men having more corticotropin-releasing hormone neurons (and having a larger posterior lobe of the pituitary) than women. Furthermore, the cortisol response to the dexamethasone suppression/

corticotropin-releasing hormone stimulation test at admission was found to vary according to the future depression outcome (symptom remission or not at five weeks of treatment) in depressed male but not female inpatients (Binder et al., 2009). Postmenopausal depressed women had higher cortisol levels after a dexamethasone test than premenopausal depressed women (Young, 1995), suggesting a gonadal-hormone-mediated association. Moreover, depressed women had higher, and men lower, evening adrenocorticotropic hormone secretion than their age- and sex-matched healthy controls (Young & Ribeiro, 2006). Lastly, women with depressive symptoms had higher levels of afternoon and evening salivary cortisol than women with no symptoms, while no difference was found between depressed and healthy men (Muhtz et al., 2009). These results are suggestive of a gender modulation of the hypothalamic–pituitary–adrenal axis function in depression.

The above-described findings may be explained by genetic polymorphisms. As an example, a specific polymorphism in the gene encoding for the α2 adrenoceptor is associated with abnormal cortisol responses in depressed men but not women, while it is the opposite in the case of the β2 adrenoceptor (Haefner et al., 2008). Another finding is that healthy men carrying the S variant of the serotonin transporter gene have higher diurnal cortisol levels, as well as lower cortisol response to morning awaking, and lower adrenocorticotropic hormone levels after the dexamethasone test, than those carrying the L variant. On the contrary, no such associations (or even opposite results) were found in (same age) healthy women (Wust et al., 2009; Wankerl et al., 2010).

Melatonin. Melatonin is a hormone produced primarily by the pineal gland. The synthesis of melatonin starts from the serotonin precursor, tryptophan, and is indirectly regulated by the light/dark cycle (Arendt, 2005). Melatonin is known to be involved in modulation of circadian rhythms (e.g., sleep and body temperature), as well as in the regulation of immune and cardiovascular functions, mood and reproductive biology (Srinivasan, 1997; Srinivasan et al., 2005). Melatonin levels and their rhythmicity seem to be altered in many psychiatric disorders, the seasonal affective disorder (which is 3.5 times more prevalent in women) being characterized by a delayed morning decrease of melatonin levels (Pacchierotti et al., 2001). However, studies are not consistent with respect to reporting a trend for higher (Rubin et al., 1992), lower (Brown et al., 1985; Khaleghipour et al., 2012) or the same (Carvalho et al., 2006) night-time melatonin levels in depressed subjects compared with healthy controls. Interestingly, Rubin and colleagues (1992) found a trend for higher night-time melatonin levels in depressed patients than in healthy controls only among premenopausal women, but not among postmenopausal women or men. Also, the offset of melatonin secretion seems to be phase-advanced in women suffering from PMS, with a consequent shorter duration and an overall lower melatonin secretion than in women with no PMS (Parry et al., 1990; Parry et al., 1997).

Gonadal hormones. The activity of many of the above-mentioned hormones and neurotransmitters varies according to menstrual cycle and reproductive phases, and is known to be modulated by gonadal steroids. The serotoninergic neurons in the mid-

brain, as well as noradrenergic and cholinergic neurons in the basal forebrain, are all targets of the estrogens. Estrogens induce a rise in serotonin (and noradrenalin) levels due to the reduced expression of monoamine oxidases and the enhanced activity of tryptophan hydroxylase, the rate-limiting enzyme of the synthesis of serotonin. Estrogens also modulate the expression and activity of the serotonin reuptake transporters and influence the distribution and regulation of serotoninergic receptors (Rubinow et al., 1998; Genazzani et al., 2007; Gasbarri et al., 2012). Similarly, progesterone has neuropsychological and neuroprotective functions, and is involved in the control of opioidergic, serotoninergic and cholinergic systems (Pluchino et al., 2009).

Jovanovic et al. (2009) found no differences in the binding potentials of serotonin receptor or serotonin transporter between the follicular and luteal phase of healthy women, while Wihlbäck et al. (2004) reported that the number and binding affinity of the platelet serotonin transporters and receptors varies according to the menstrual cycle phase and is correlated with the concentrations of estrogen and progesterone. Baca-Garcia et al. (2003b) studied the interaction between estrogens and the gene of the serotonin transporter in determining the risk of attempted suicide. Women with the S allelic variant of the serotonin transporter gene (with lower serotoninergic activity) are *per se* at higher risk of suicide, a diminished serotoninergic activity being associated with high suicidal risk (Mann, 1998). However, Baca-Garcia and colleagues (2003b) found that women with the L gene variant are more sensitive to the reduction in estrogen levels (which leads to a consequently diminished serotoninergic activity), and thus are more vulnerable to suicide during the low estrogen phases (i.e., premenstrually and in menopause).

Melatonin production is also partly regulated by sex hormones. Receptors for gonadal hormones have been found in the human pineal gland (Luboshitzky et al., 1997), and receptors for melatonin in the human ovaries (Niles et al., 1999). Moreover, even though the level of melatonin seems not to vary with the menstrual cycle phase, it has been found to be higher when estrogen levels are lower (e.g., in the case of amenorrhea) (Brzezinski et al., 1988), as well as in women using oral contraception (Kostoglou-Athanassiou et al., 1998).

These and several other findings provide evidence for the gender-dependent role of gonadal steroids as factors contributing to the pathogenesis of psychiatric disorders.

2.4 Endogenous and exogenous gonadal hormones

2.4.1 Physiology of the reproductive cycle

During fetal life levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) are high, almost equal to the postmenopausal levels. At birth they stay high for a few months and years, respectively; they subsequently decrease and remain low and stable until puberty.

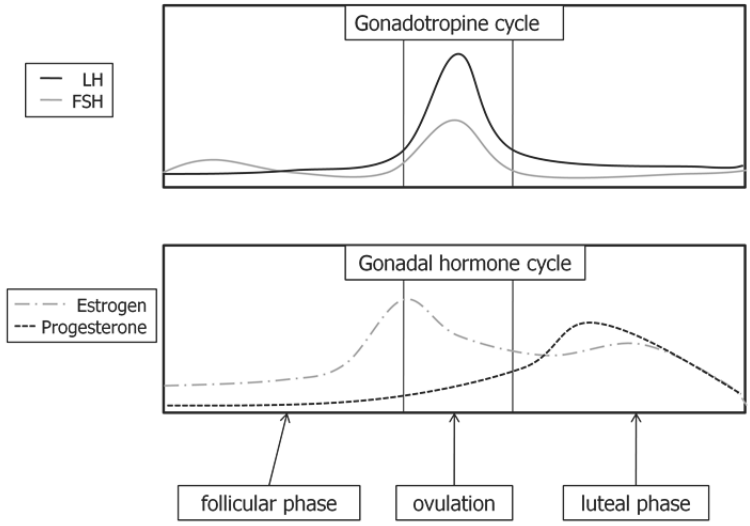
Puberty. Puberty is a sequence of events leading to physical and psychological changes resulting in adult physical characteristics and the capacity to reproduce. In girls the first visible change of puberty is usually the breast development, followed by the growth of pubic and axilla hair. The first menstrual period generally occurs between 12 and 13 years.

It is not completely clear which mechanisms are involved in the initiation of puberty. Central influences may inhibit release of the gonadotropin-releasing hormone during childhood, and stimulate its release to induce puberty in early adolescence. The hypothalamus secretes gonadotropin-releasing hormone, which regulates the release of the gonadotropins LH and FSH from the anterior pituitary gland. These hormones induce ovulation and the consequent secretion of the sex hormones estradiol and progesterone from the ovaries, which in turn stimulate the target organs of the reproductive system.

Menstrual Cycle. The average duration of the menstrual cycle is 28 days; it begins and ends with the first day of menses. The menstrual cycle consists of follicular (preovulatory), ovulatory, and luteal (post-ovulatory) phases (Figure 3).

Follicular phase. This phase is the less constant in its duration. In the early follicular phase the levels of LH and FSH in the anterior pituitary are low, as it is the production of estrogen and progesterone. FSH secretion increases slightly; also, circulating LH levels rise slowly, starting from one to two days following the increase in FSH. The production of estradiol from the recruited ovarian follicles increases rapidly; this leads to increased synthesis, but reduced secretion, of LH and FSH. During the second half of the follicular phase (late follicular phase) FSH levels decrease, while LH levels are affected less. This is partly because estradiol inhibits FSH more than LH secretion. In addition, the hormone inhibin is produced by the developing follicles. This hormone is able to inhibit FSH but not LH secretion. Levels of estrogen, particularly estradiol, increase exponentially.

Ovulatory phase. It is characterized by the occurrence of ovulation. Estradiol levels usually peak at the beginning of this phase. Progesterone levels also increase. The LH surge (i.e., a massive release of stored LH) occurs, while FSH levels increase at a smaller amount. The LH surge is also stimulated by high levels of estradiol (positive feedback), by gonadotropin-releasing hormone and progesterone. During the LH surge, estradiol levels decrease, while progesterone levels continue to increase.



Abbreviations: Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH).

Figure 3. Gonadotropine and gonadal hormone cycles

Luteal phase. The follicle is transformed into a corpus luteum. This phase is the most constant in its duration, usually 14 days, after which the corpus luteum degenerates. Increasing quantities of progesterone are released primarily by the corpus luteum. Levels of circulating estradiol, progesterone, and inhibin are high during most of the luteal phase; consequently, LH and FSH levels decrease. Estradiol and progesterone levels decrease late in this phase.

Menopause. The permanent end of menstrual periods, and of fertility, is called menopause. As women age, the production of estrogens and progesterone from the ovaries gradually decreases; thereby menstrual periods and ovulation occur less often. Eventually, when the complete depletion of active follicles occurs, the menstrual periods and ovulation cease permanently. This leads to the absence of estrogen negative feedback: consequently, FSH and LH levels rise significantly, reaching concentrations that are 13 times and 3 times higher, respectively, than normal early follicular phase concentrations.

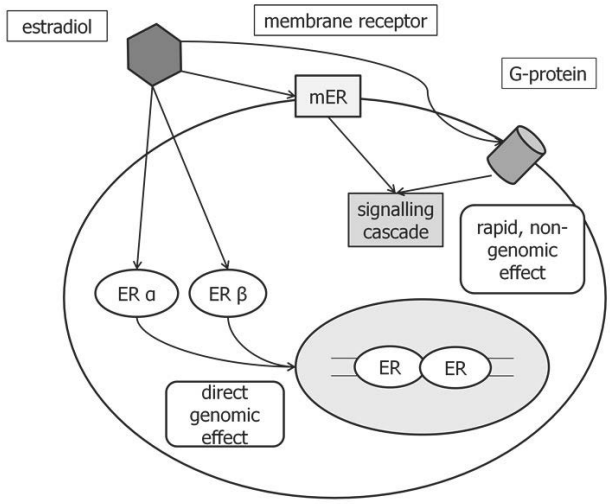
The term "perimenopause" identifies a specific transitional period which occurs during the years before and the year after the last menstrual period. The perimenopause is characterized by marked fluctuations in the levels of estrogen and progesterone. In perimenopause there is also a marked elevation of early follicular-phase FSH levels, not always followed by a rise in LH levels (Sherman et al., 1976). These fluctuations probably cause the menopausal symptoms experienced by many women in their

40s and 50s (flushes, sweating, palpitations, tachycardia). The entire transition takes a period of 10 to 15 years (Morrison et al., 2006).

2.4.2 Estrogens, progesterone and the central nervous system

The effects of gonadal hormones (i.e., estrogen, progesterone and testosterone) on the central nervous system are evident already during fetal life. Indeed, gonadal steroids are partly responsible for the sexual brain differentiation and, after the development of gonads, they drive specific organizational and developmental changes in the brain. The testosterone produced by the male gonads is converted into estradiol: in this way it is able to bind the estrogen receptors in the developing brain, leading to masculinisation and defeminisation of the male brain. Conversely, in the female fetus, the maternal estrogens are bound by the α-fetoprotein, thus preventing masculinisation–defeminisation of the female brain (Lenz et al., 2010). Thus, sexual differentiation of the brain starts in the second semester of pregnancy and continues until adulthood (Swaab, 2007). In the adult brain estrogen and progesterone receptors are widely expressed. Estrogen receptors are present not only in the hypothalamus (where they mostly control the reproductive function), but also in the hippocampus (known to be sexually differentiated), amygdala, locus coeruleus, cerebellum, as well as in the pituitary, basal forebrain, cerebral cortex and glial cells (Genazzani et al., 2007). Moreover, cholinergic, noradrenergic, serotoninergic and dopaminergic neurons also respond to estrogens and progesterone. It is of note that the effects of gonadal hormones change depending on the type of receptor they bind to. Indeed, binding to the nuclear receptors α and ß leads to a delayed and prolonged "genomic" effect. Target genes include those encoding for neurotransmitters, enzymes and receptors (possibly with differences between men and women). Conversely, binding to membrane receptors leads to rapid, "non-genomic" effects which include the activation of cascades of signals (involving a variety of second messengers) (Rubinow et al., 1998; Genazzani et al., 2007) (Figure 4).

In this way, a high number and variety of cells in the brain are estrogen-responsive. However, it is worth remembering that each brain region, or even each cell in the same brain region, may express different estrogen receptors leading to different responses; moreover, the same receptor may activate different signals and pathways. Furthermore, since the non-genomic effects require the actions of second messengers, and since the second messengers may differ from tissue to tissue, it is possible that the same hormone, even binding to the same type of receptor, leads to different effects depending on the target tissue (e.g., to stimulation or rather inhibition of the same neurotransmitter). That is, the final response to a gonadal steroid is extremely complex and depends on "the context", i.e. type of receptor and presence and type of co-regulators (Rubinow, 2005).



Abbreviations: Estrogen Receptor (ER), membrane Estrogen Receptor (mER).

Figure 4. Estrogen receptors and their mechanisms of actions.

2.4.3 Hormonal contraception and mental health

The widespread use of hormonal contraception and replacement therapy has brought the question of possible effects of exogenous estrogens and progestins in women.

A great amount of research has been focused on side effects and beneficial effects of hormonal contraceptives, with the general conclusion that oral contraceptive (OC) use is associated with several health benefits, such as lower risks of endometriosis, and of endometrial and ovarian carcinoma (Maia & Casoy, 2008; Braem et al., 2010). However, little is known about the effects of hormonal birth control on mental health. It is likely that contraception *per se* has a beneficial psychological effect as women do not need to be afraid of an unplanned pregnancy. On the other hand, due to their several brain effects, the contraceptive steroids as well as their downstream endocrine effects may have consequences on mood and anxiety. In this respect, the findings reported in the literature are contradictory and inconsistent. In an earlier study by Herzberg et al. (1971), it was reported that mean depression scores decreased in women continuing the use of an intrauterine device (IUD) or an OC, while they increased in women stopping or changing OCs. More recent studies have shown no significant association between OC use and depression (Duke et al., 2007; O'Connell et al., 2007). Rapkin et al. (2006) found no relationship between OC-induced reduction in the concentrations of circulating neuroactive steroids and mood or anxiety symptoms in healthy women. Nevertheless, depression is often mentioned as a possible side-effect of OCs as well as of hormonal contraceptive implants or injections, and women continue to report depression and other mood changes as common reasons for discontinuation of OCs

(Oinonen & Mazmanian, 2002). It has been suggested that mood and affective changes such as OC side effects may occur in a subgroup of vulnerable women (Oinonen & Mazmanian, 2002; Rapkin et al., 2006). In particular, one hypothesis claims that women who experience side effects of OCs are more sensitive to hormonal changes (Bird & Oinonen, 2011) since they have been found to be at higher risk of postpartum depression (Bloch et al., 2005) and distress at menopausal transition (Stewart & Boydell, 1993). Moreover, women who develop mood symptoms as a side effect of OCs are more likely to suffer from eating disorder symptoms (Bird & Oinonen, 2011) and to be characterized by specific personality traits, such as somatic anxiety and stress susceptibility (Borgström et al., 2008). Lastly, women who suffered from affective changes while taking combined oral contraceptives (COCs) are at risk of further depressive symptoms during a following COC cycle (Gingnell et al., 2012).

Information concerning the possible side effects of the levonorgestrel-releasing intrauterine system (LNG-IUS) on mental health is even scantier. Since its introduction in the 1990s, it has been increasingly used in contraception as well as in the treatment of heavy menstrual bleeding worldwide. Studies concerning acceptability and the reasons for and rates of discontinuation indicate bleeding problems, amenorrhea and hormonal adverse effects as possible consequences of use of the LNG-IUS (Rönnerdag & Odlind, 1999; Inki, 2007). The majority of the studies report that LNG-IUS users experience a significant improvement in their quality of life and psychological well-being (Skrzypulec & Drosdzol, 2008), with satisfaction rates ranging from 50% (Daud et al., 2008; Ewies, 2009) to 90% (Römer & Linsberger, 2009), both in the case of consecutive use of the LNG-IUS either for contraception or for the treatment of heavy menstrual bleeding (Römer & Linsberger, 2009; Heikinheimo et al., 2010). In a Finnish survey on premature removal of the LNG-IUS, bleeding disorders were the main reason for discontinuation (Backman et al., 2000). However, mild and rare hormonal side effects have been reported, such as nausea, breast tenderness, headache, skin problems, mood changes and nervousness (Luukkainen, 1991; Luukkainen et al., 1990; Luukkainen et al., 2001), and in a study carried out in India to analyze the use of the LNG-IUS as a treatment for menorrhagia, 8% of the users reported mood changes and 3% reported depression as a side effect of the LNG-IUS (Kriplani et al., 2007). However, to the best of our knowledge, no study has specifically been focused on the effects of the LNG-IUS on mental health.

2.4.4 Hormone therapy in peri- and postmenopausal women

Even though the majority of women do not develop depressive symptoms or disorders in connection with the menopausal transition, a subgroup seems to be vulnerable to mood impairment during the perimenopause, with 15% to 50% of perimenopausal women experiencing depressive symptoms (Clayton et al., 2008; Timur & Sahin,

2010). As already said, the risk of perimenopausal depression seems to be higher during the late stage of the menopausal transition, i.e. when the estrogen withdrawal is more significant (Schmidt et al., 2004; Steinberg et al., 2008). Therefore, it would be intuitive to hypothesize that, if the estrogen withdrawal is a contributing factor to perimenopausal depression in vulnerable women, estrogen therapy (ET) and/or combined estrogen plus progestogen therapy (EPT) would be of help in preventing or attenuating the correlated symptomatology. Indeed, ET has been suggested as an antidepressant agent or as an augmentation strategy for peri- and postmenopausal depression. Some studies have shown a beneficial effect of ET on psychological well-being and quality of life (Wiklund et al., 1993; Karlberg et al., 1995), as well as on the treatment of depressive disorders (Soares et al., 2001) in perimenopausal and postmenopausal women. The latter study showed transdermal estradiol to be effective in treating MDD, minor depressive disorder and dysthymic disorder in perimenopausal women independently of its effects on climacteric symptoms. This was consistent with a similar report of reduced depressive symptoms in perimenopausal women with a diagnosis of major or minor depressive disorder irrespectively of climacteric symptoms such as hot flushes (Schmidt et al., 2000). However, other studies have failed to find any mood improvement with estrogen-only therapy in depressed peri- and postmenopausal women (Coope, 1981; Morrison et al., 2004).

As far as it concerns combined EPT, in a randomized controlled trial Hlatky and colleagues (2002) found a more notable improvement of depressive symptoms among women assigned to EPT than to placebo, and postmenopausal depressed EPT or ET users seem to have a better response to selective serotonin reuptake inhibitors than women using no hormone therapy (HT) (Zanardi et al., 2007). However, there is some inconsistency on this issue. Indeed, the effects of progestogens on mood are quite questionable, and it seems that they may counteract the positive estrogenic effects and even induce depressive mood swings (Sherwin, 1999). In the above-mentioned study by Hlatky et al. (2002), women complaining of postmenopausal symptoms (i.e., flushing) had an amelioration of their mental health and depressive scores with EPT; on the contrary, EPT use was associated with poorer quality of life in terms of physical functioning and energy score. On this respect, it must be kept in mind that unopposed estrogen cannot be administered to women with an intact uterus, due to an increased risk of endometrial hyperplasia (Writing Group for the PEPI Trial, 1996). Therefore, a combination of estrogen plus progestogens is required in non-hysterectomized women.

In conclusion, female gonadal hormones affect multiple sites in the central nervous system. Also, several unquestionable benefits for women's health come from the use of exogenous hormones in terms of both contraception and replacement therapy. Even though the nature of these benefits is partly intuitive – as in the case of beneficial correlates of not having to be worried about unwanted pregnancies – there is still quite a debate on the effects that exogenous hormones, in different forms and combinations, may have on mental health *per se*.

3 Aims of the study

The aim of this study was to investigate the associations between mental health and psychological well-being of women in relation to their reproductive features. The main research questions and hypotheses were the following:

I *Is a history of miscarriage related to further impairment of mood or psychological well-being? If so, is this impairment related to an increasing number of miscarriages?*
The main hypothesis was that there is a relationship between pregnancy outcome and women's mental health or psychological well-being. Specifically, having had one or more miscarriages is associated with depressiveness, suicidal ideation and other psychiatric symptoms. Also, it was hypothesized that the higher the number of miscarriages, the worse the psychological status even in the long-term (Study I).

II *Does hormonal contraception have any influence on mental health or psychological well-being? Do different hormonal compounds differently influence mental health? Is the duration of use of hormonal contraception related to mental health?*
The main hypothesis was that use of hormonal contraception (and its duration) is not associated with a worsening of women's psychological status or with an increased risk of psychiatric diagnoses. Different psychological effects are expected depending on the type of hormonal contraceptive (OC vs. LNG-IUS) and its composition (second vs. third generation OCs) (Studies II and III).

III *Does hormone therapy in perimenopausal and postmenopausal women have any influence on mental health or psychological well-being? Do the relationships, if any, differ accordingly to different hormonal compounds?*
The main hypothesis was that use of hormone therapy (either estrogen-only or combined estrogen plus progestogen) is not associated with a worsening of women's mental health; rather, it may positively affect mood and psychological well-being. Different patterns are expected depending on the composition and route of administration. Better mood effects are expected in the case of estrogen-only than in the case of combined therapy (Study IV).

4 Subjects and methods

4.1 Materials

The data analyzed in this work were gathered from two Finnish population-based studies, namely the Health 2000 and the FINRISK Surveys 1997, 2002 and 2007. Data from the four surveys were differently combined, according to the aim of each study. Data sources for each study are summarized in Table 4.

Table 4. Surveys used in Studies I, II, III and IV.

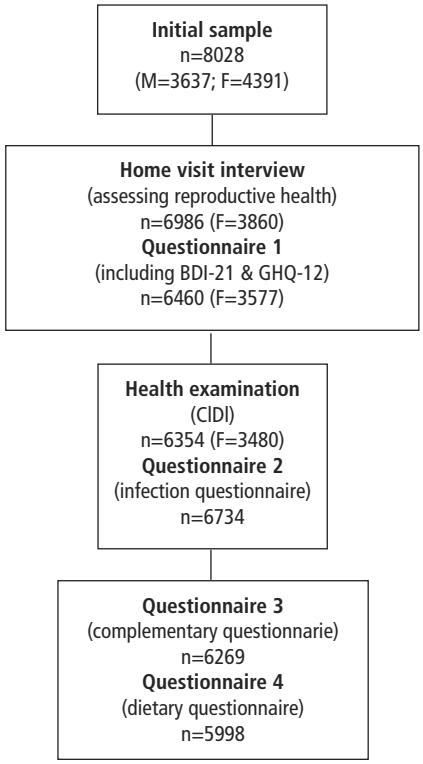
	Health 2000	FINRISK 1997	FINRISK 2002	FINRISK 2007
Study I	X		X	
Study II	X			
Study III		X	X	X
Study IV	X	X	X	X

4.1.1 Health 2000

Health 2000 was a cross-sectional, nationwide, population-based survey. It was carried out in Finland in 2000 to 2001 (www.terveys2000.fi) through a stratified and clustered sampling procedure. In this way it was possible to obtain a representative sample (n=8028; final sample n=6986; males=3126, females=3860) of the general population aged 30 years and older (Heistaro, 2008). Data were collected via a home interview and a clinical health examination. A total of four self-administered questionnaires were also given to be filled and returned. One of the self-administered questionnaires included a modified version (Raitasalo, 1977; in http://www.terveys2000.fi/doc/methodologyrep.pdf) for the Finnish population of the 21-item Beck Depression Inventory (BDI-21) and the General Health Questionnaire-12 (GHQ-12). Mental health in the previous 12 months was assessed during the health examination via the Composite International Diagnostic Interview (CIDI), a structured mental health interview (Wittchen et al., 1998) (Figure 5).

A separate study was carried out on a random sample of young adults aged 18 to 29 years (n=1894). For these, data collection consisted of a home interview and two self-reported questionnaires (including the GHQ-12 questionnaire).

The survey was approved by the Ethics Committee of the National Public Health Institute (1999) and by the Ethics Committee for Research in Epidemiology and Public Health at the Hospital District of Helsinki and Uusimaa (2000). All participants gave written informed consent.



Abbreviations: Beck Depression Inventory-21 items (BDI-21), Composite International Diagnostic Interview (CIDI), General Health Questionnaire-12 items (GHQ-12).

Figure 5. Health 2000: design of the study.

4.1.2 National FINRISK Survey

The National FINRISK Study Survey is a cross-sectional, population-based health survey carried out in Finland every five years since 1972 (www.ktl.fi/finriski). The participants were selected through random sampling of the population from the Finnish Population Information System; a gender-, area-, and 10-year age group- stratification was applied.

The FINRISK-97 study covered five geographical areas of Finland (Helsinki region, south-western Finland, North Karelia, the region of Kuopio and the province of Oulu). Its target population was a random sample of people aged 25 to 64 years (n=10 000); additionally, a smaller sample (n=750) of persons aged 65 to 74 years was included from two areas. Data for the FINRISK 2002 and 2007 were collected from the cities of Helsinki and Vantaa, the areas of Turku and Loimaa, and the provinces of North Savo, North Karelia, Oulu and Lapland. Data were gathered from a population aged 25 to

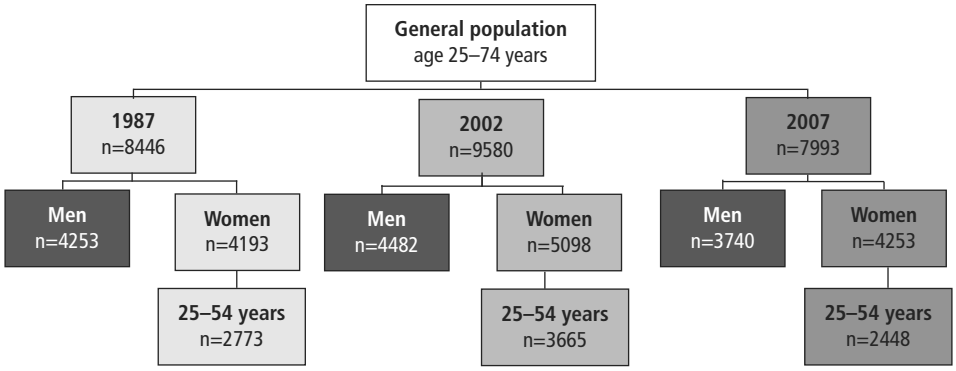


Figure 6. FINRISK Surveys 1997, 2002 and 2007: design of the study.

64 years in FINRISK 2002, and 25 to 74 years in FINRISK 2007. In FINRISK 2002, additional data for people aged 65 to 74 years were also available from the cities of Helsinki and Vantaa and the province of Lapland (Figure 6).

The survey consisted of a self-administered questionnaire and a health examination. Additionally, women participating in FINRISK 2002 were asked to complete an additional questionnaire inquiring in more detail into their reproductive health.

The FINRISK survey complied with the ethical rules of the National Public Health Institute and the Declaration of Helsinki. Ethics approval was received from the coordinating Ethics Committee of the Helsinki University Hospital District.

4.2 Methods

4.2.1 Variables of interest: reproductive health

4.2.1.1 Health 2000

Data on reproductive health features were collected systematically during the non-structured, lay-administered interviews. The questions included information on menstrual features, pregnancies, infertility, past and current use of contraception and HT, and duration of its use.

Bleeding pattern and current use of hormonal contraceptives were investigated in the 30- to 54-year-old group. The length of time of hormonal birth control use was also specified, along with the current brand of OC. The current use of hormonal contraception and its duration, as well as the current brand of OC, were also assessed among young women (aged 18 to 29 years).

History of hysterectomy was assessed by asking if the woman had had a hysterectomy and whether the uterus and both ovaries, or the uterus and one ovary, or only the uterus was removed.

Women's reproductive status was classified as postmenopausal if time from the last period was 12 or more months; perimenopausal, if it was between 6 and 12 months or if the woman was using HT (and the periods have not ended before starting HT); and premenopausal, if the time since last period was less than six months.

4.2.1.2 National FINRISK Survey

The questions concerning reproductive health included information on menstrual cycle, pregnancies, infertility, past and current use of contraception and HT, and duration of its use. The questions were similar to those used in the Health 2000 study.

History of hysterectomy was assessed via the question "Have you undergone a hysterectomy?", with possible answers "no"; "yes, removal of uterus and ovaries"; and "yes, removal of uterus and one ovary at most" (1997 and 2007). With regard to FINRISK 2002, the information was extrapolated from the question "If your menstruation has ended, did it end …", with possible answers including "because of hysterectomy (at least one remaining ovary)" and "because the uterus and both ovaries were removed".

Premenopausal women were identified via the questions "Do you still menstruate?" with possible answers "yes, regularly", "yes, irregularly" and "no, my last period was … years ago" (FINRISK 1997 and 2007), and "If your menstruation has ended, did it end…?", with possible answers including "my menstruation has not ended" (FINRISK 2002). Thus, a clear distinction between perimenopausal and postmenopausal women was not available.

The questions used to assess women's reproductive features in the Health 2000 and FINRISK Surveys are reported in Table 5.

Table 5. Questions used to assess reproductive health in Health 2000, FINRISK 1997, 2002 and 2007.

	Health 2000	FINRISK 1997	FINRISK 2002	FINRISK 2007
Age at menarche	How old were you when your periods started?	---	How old were you when you started menstruating?	---
Menstrual cycle regularity	Do you have periods nowadays -> • regularly • irregularly • none	Do you still menstruate? -> • yes, regularly • yes, irregularly • no	Have you ever had menstrual irregularity? Do you at the moment experience the need to find help to solve or alleviate your menstrual irregularity?	Do you still menstruate? -> • yes, regularly • yes, irregularly • no
Duration of menstrual cycle	---	How long usually is/was your menstrual cycle (the time from the first menstruation day to next period's menstruation day)?	How long does it/did it take between the beginning of your menstruation to the beginning of your next menstruation?	How long does/did it take between the beginning of your menstruation to the beginning of your next menstruation?

	Health 2000	FINRISK 1997	FINRISK 2002	FINRISK 2007
Duration of menstrual bleeding	---	How many days do/ did you normally menstruate?	How many days do you usually menstruate/ used to menstruate?	How many days do/ did you usually menstruate?
Age at menopause	When was your last period?	Do you still menstruate? -> • yes, regularly • yes, irregularly • no, my last period was __ years ago	If your menstruation has ended, did it end: -> • naturally to the menopause (year) • because of hysterectomy (at least one remaining ovary) (year) • because the uterus and both ovaries were removed (year) • because of radiotherapy or other reason (year)	Do you still menstruate? -> • yes, regularly • yes, irregularly • no, my last period was __ years ago
Cause of menopause	Did your periods end: -> • naturally with the menopause • after an operation or radiotherapy • for some other reason (e.g. because of hormone medication)	---	If your menstruation has ended, did it end: -> • naturally to the menopause • because of hysterectomy (at least one remaining ovary) • because the uterus and both ovaries were removed • because of radiotherapy or other reason	---
Number of pregnancies	How many pregnancies have you had?	---	How many times have you been pregnant?	---
Number of (live) births	How many children have you delivered? How many were born alive?	How many children have you born?	How many births have you had?	Have you given birth to a child/children? -> • no • yes (year)
Number of living children	How many living children do you have at the moment, including adopted children, children whose foster parent you are and other "non biological children"?	---	How many living children do you have (include adopted and foster children and also other "non-biological" children)?	How many children do you have (including adopted children, foster children and other "non-biological" children)?
Miscarriages	How many miscarriages have you had?	---	Have you had miscarriages? How many?	---
Abortions	How many abortions have you had?	---	Have you had abortions? How many?	---
Infertility	Have you had such time periods, when you have tried to get a child, but have not succeeded or to succeed has taken over 12 months?	---	Was there ever a time period when you tried to become pregnant but pregnancy did not begin or it has taken over 12 months?	Have you ever had trouble becoming pregnant and having children?
Treatment for infertility	Have you been in examinations because of childlessness/infertility or received treat-ment for it?	Have you had hormone therapy to treat childlessness?	Have you ever been examined or been treated for infertility?	If you have had trouble becoming pregnant and having children, have you consulted a doctor?

	Health 2000	FINRISK 1997	FINRISK 2002	FINRISK 2007
OC use	Do you at the moment take contraceptive pills? Have you used contraceptive pills earlier? What is the name of the preparation you are using now?	Are you presently on the contraceptive pill? (name of the product)	Do you at present use contraceptive pills? Have you previously used contraceptive pills?	Have you used or do you at present use contraceptive pills?
Duration of OC use	During how many years altogether have you been taking contraceptive pills?	Are you presently on the contraceptive pill?-> • yes, I have used the pill for __ years • no, but I have earlier used it for __ years • I have never used it	How many years have you altogether used (now or earlier) contraceptive pills?	Have you used or do you at present use contraceptive pills? -> • yes, I do at present and I have used them for __ years • no, but I have previously used them for __years • no, I have never used them
LNG-IUS use	For birth-control, are you at the moment using a hormonal intrauterine device (IUD)? Have you some time earlier used a hormonal IUD?	Do you presently use a hormonal IUD?	Do you at present use as contraception a hormonal IUD? Have you earlier used hormonal IUD for contraception?	Have you used or do you at present use a hormonal IUD for contraception?
Duration of LNG-IUS use	For how many years altogether have you been using a hormonal IUD?	Do you presently use a hormonal IUD? -> • yes, I have used it for __ years • no, but I have earlier used it for __ years • I have never used it	How many years have you altogether (now or earlier) used hormonal IUD?	Have you used or do you at present use a hormonal IUD for contraception? -> • yes, I do at present and I have used it for __ years • no, but I have previously used it for __ years • no, I have never used it
HT use	Have you, because of the menopause or of hormone deficiency after the menopause, used hormone replacement therapy as tablets, gel or sticking plaster during the past month? Have you earlier used hormone replacement therapy because of the menopause or deficiency of hormones after the menopause? What is the name of the preparation you are using now?	Have you used hormone replacement therapy as tablets, gel or patches during the past month?	Have you used hormone replacement therapy for menopause or menstruation trouble for the last 6 months? Have you earlier used hormone replacement therapy for menopause or menstruation trouble?	Have you used hormone replacement therapy in the form of tablets, gel or patches for the last 6 months? (name of the product)
Duration of HT use	For how many years have you been using hormone replacement therapy?	How long have you used hormone replacement therapy?	For how many years have you used hormone replacement therapy?	How long have you used hormone replacement therapy?

Abbreviations: Hormone Therapy (HT), Intrauterine Device (IUD), Levonorgestrel Intrauterine System (LNG-IUS), Oral Contraceptive (OC).

4.2.2 Outcome variables: mental health

Mental health was assessed via structured (GHQ-12, BDI-13, BDI-21) and non-structured self-administered questionnaires and via a lay-administered, structured interview (CIDI). Different questionnaires and interviews were used in the Health 2000 and FINRISK Surveys (Figures 7 and 8).

4.2.2.1 Beck Depression Inventory (BDI)

The presence and severity of depressive symptoms in the previous 2 weeks were assessed via a modified version of the 21-item (Raitasalo, 1977) (Health 2000, FINRISK 1997) and 13-item (Raitasalo, 2007) (FINRISK 2007) BDI, a reliable and commonly used (Beck et al., 1988) self-reported inventory validated by Beck et al. (1961) to assess depression by inquiring specifically into depressive, cognitive and somatic symptoms. The 21-item BDI score ranges from 0 to 63, with scores of 10–16 indicating mild, 17–29 moderate and 30–63 severe depressive symptoms. The BDI short form, Finnish version, includes 13 out of the 21 original items (sadness, future hopelessness, past failure, dissatisfaction, self-disappointment, uselessness, suicidal ideation, lost interest in people, indecisiveness, feeling of looking ugly, impaired working capability, tiredness, and lost appetite). Its total score ranges from 0 to 39, with scores of 5–7 indicating mild, 8–15 moderate and 16–39 severe depression. BDI total scores were considered only for the cases with at least 16 (BDI-21) and 10 (BDI-13) valid answers (as in Raitasalo, 2007). In the case of missing values, the adjusted total score was calculated with the following algorhythms (Raitasalo, 2007):

- BDI-21: (score for questions answered/number of questions answered) x 21;
- BDI-13: (score for questions answered/number of questions answered) x 13.

In addition, each BDI-item score was calculated for all the participants with a valid answer for that item.

No BDI evaluation was available in FINRISK 2002.

4.2.2.2 General Health Questionnaire (GHQ)

Psychological well-being was assessed in the Health 2000 survey via the 12-item GHQ, a broadly used questionnaire introduced by Goldberg (1972) to evaluate the common mental state, with particular attention to the areas of depression and anxiety. The GHQ-12 gives a view of recent general mental health (in the past 4 weeks). GHQ-12 total score ranges from 0 to 12 (binary scoring method, with the two least symptomatic answers scoring 0 and the two most symptomatic answers scoring 1), with 3 being the threshold for psychiatric caseness. GHQ-12 total scores were considered only for the cases with at least 10 valid answers. In the case of missing values, the adjusted total score was calculated with the following algorhythm:

- (score for questions answered/number of questions answered) x 12.

In addition, each GHQ-12-item score was calculated for all the participants with a valid answer for that item. The validity and reliability of the GHQ-12 have been widely demonstrated (Goldberg et al., 1976).

4.2.2.3 Composite International Diagnostic Interview (CIDI)

At the end of the health examination in the Health 2000 survey a structured diagnostic interview (CIDI) developed by the World Health Organization (1990) was carried out. The CIDI is a comprehensive, fully structured diagnostic interview based on the definitions and criteria of the International Classification of Diseases 10 and DSM-IV. It is designed to be administered by trained lay interviewers, and it allows assessment of the presence, onset and recentness of psychiatric disorders (lifetime and in the 12 months prior to the interview). It has been demonstrated to have excellent reliability and adequate validity (Andrews & Peters, 1998). The Munich computerized version of the CIDI was used (Wittchen et al., 1998). For the purpose of this study, the focus was on alcohol abuse and dependence, MDE, MDD, dysthymic disorder, any anxiety disorder (i.e. panic disorder with or without agoraphobia, social phobia, phobic disorder not-otherwise-specified or generalized anxiety disorder). "Any current psychiatric diagnosis" was defined as meeting the criteria for at least one full diagnosis in the last 12 months (excluding cases with missing data at one or more of the diagnoses inquired about).

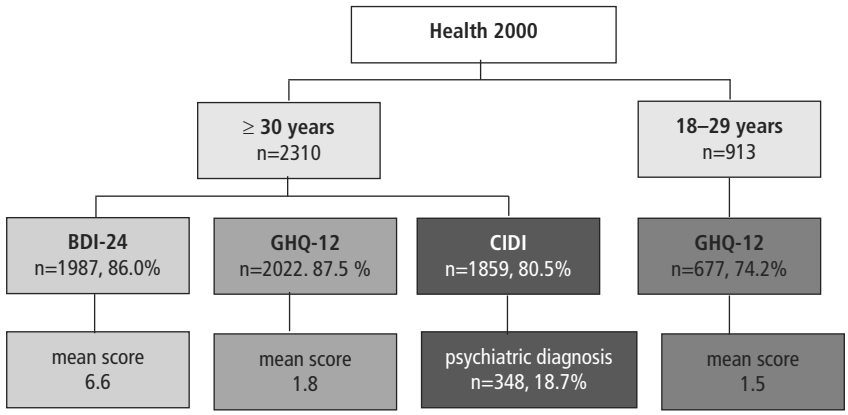
4.2.2.4 Self-reported psychiatric diagnoses and psychotropic drug use

No structured diagnostic interview was carried out in connection with the FINRISK surveys. However, participants in FINRISK 2002 and 2007 were asked if they had received a psychiatric diagnosis in the previous year: "Has a doctor diagnosed or treated you for depression or other psychological illness during the past year (last 12 months)?" Additionally, information on the use of any psychotropic drug during the previous year was available for FINRISK 1997 ("When was the last time you used sleeping pills/tranquillizers/antidepressants?", with possible answers "during the past week", "1–4 weeks ago", "1–12 months ago", "over a year ago" and "never").

4.2.2.5 Other psychological symptoms

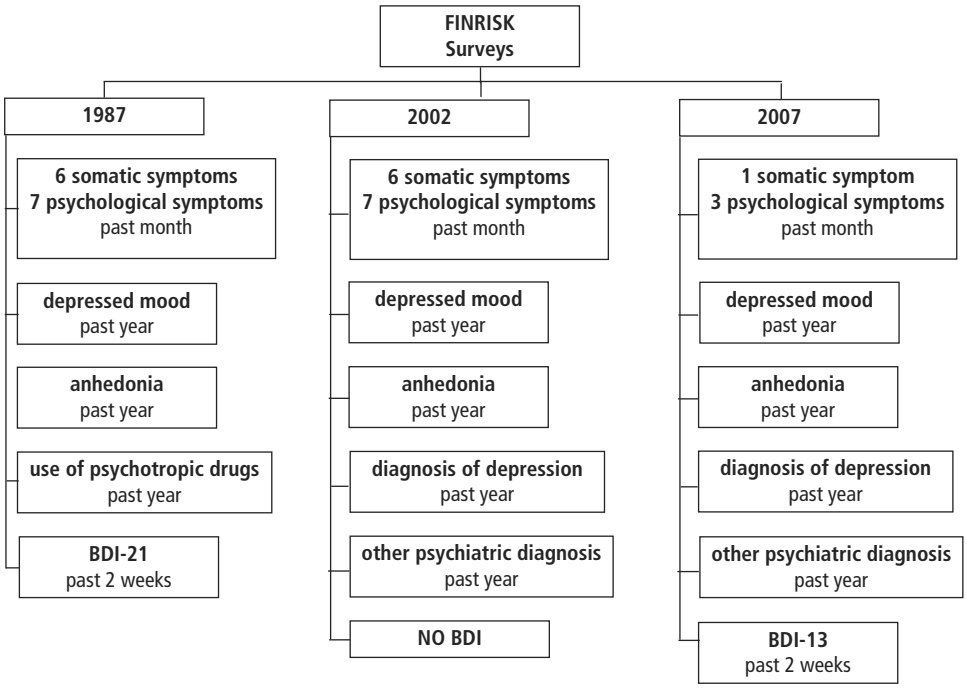
In the FINRISK surveys additional non-structured questionnaires were carried out to better assess psychological well-being. The presence of somatic and psychological symptoms was evaluated by asking the participants how often ("often, sometimes, not

at all") in the previous month they had had one or more of 13 somatic and psychological symptoms. Somatic symptoms included tachycardia, trembling of the hands, irregular heart rate, dizziness, headache and sweaty palms. Psychological symptoms included feeling confused when having to do something quickly, feeling tense and nervous, having frightening thoughts, feeling exhausted and overstrained, having nightmares, depressiveness and insomnia. Only four symptoms (feeling exhausted, having nightmares, insomnia and headache) were inquired about in FINRISK 2007. Additionally, the presence of depressed mood and anhedonia in the previous year was assessed via the questions "Have you during the last 12 months had a period of at least two weeks, when you have for the most time been low-spirited or depressed?" and "Have you during the last 12 months had a period of at least two weeks, when you have for the most time lost interest in most things, such as hobbies, work, or other things that usually give you pleasure?".



Abbreviations: Beck Depression Inventory-21 items (BDI-21), Composite International Diagnostic Interview (CIDI), General Health Questionnaire-12 items (GHQ-12).

Figure 7. Health 2000: mental health assessment (women).



Abbreviations: Beck Depression Inventory (BDI), Beck Depression Inventory-13 items (BDI-13), Beck Depression Inventory-21 items (BDI-21).

Figure 8. FINRISK Surveys: mental health assessment.

4.2.3 Statistical analyses

Bivariate analyses were performed in all the studies to test the difference between groups, using "history of miscarriage" (Study I), "current use of OCs" and "current use of the LNG-IUS" (Study II and III), and "current use of HT" (Study IV) as grouping variables. The $\chi 2$ test was used to compare frequencies in tables and Fisher's exact test was selected when expected frequencies were less than five. For continuous variables, comparisons of means were carried out using Student's t-test. A two-tailed *p*-value <0.05 was considered significant.

The existence of partial correlations (age as a controlling variable) between mental health and reproductive health variables was investigated in each study.

Multivariable analyses were performed, using linear and logistic regression models or generalized linear models, as appropriate, in order to identify the predictors that had a significant association with each mental health outcome variable. Predictors of interest included history (yes or no) and number (as a linear variable) of miscarriag-

es (Study I), use (yes or no) of OCs or the LNG-IUS, and the length of time of use (Study II and III), and current use (yes or no) of HT (Study IV). Sociodemographic characteristics (age, professional status, marital status, educational level), reproductive features (bleeding pattern, number of (live) births, number of living children, experience of having given birth, lifetime infertility, reproductive status, history of hysterectomy) and current psychiatric diagnosis were entered in the models as controlling variables when appropriate, as described in the original publications. In study II the effects of third-generation (those containing desogestrel or gestodene) vs. second-generation (i.e. those containing levonorgestrel, norgestimate or cyprotereone acetate) COCs were further analyzed through additional regression models where the type of OC was also entered as a predictor. Similarly, in study IV the possible effects of different preparations (estrogen-only vs. combined preparations; oral estrogens vs. parenteral estrogens, and cyclic preparations vs. continuous combined preparations) were tested with three additional regression models. For this purpose, three categorical variables (indicating the type of HT preparation) were created and alternatively entered in the regression models as further predictors.

Results are presented in terms of ORs and non-standardized B values with their 95% CIs, indicating the factor by which the risk of a single symptom/disorder, or the score at a specific scale, is increased or decreased in the case of a history of miscarriage, or by each increasing miscarriage (Study I), in the case of OC or the LNG-IUS use, and with increasing duration of its use (Study II and III), and in the case of use of HT (Study IV). Cases with missing data concerning one or more variables were omitted from the analyses.

Descriptive and multivariable analyses were performed using SPSS/PASW software (version 18.0) (SPSS Inc., Chicago, IL, USA).

5 Results

5.1 Main findings

The main findings with regard to associations between mental health and reproductive features in women are presented in Table 6.

Miscarriage as a pregnancy outcome was related to a high prevalence of depressive symptoms and disorder and more severe depressive/anxiety symptoms compared with other pregnancy outcomes. Moreover, the higher the number of miscarriages, the worse the current state of mood was and the higher the frequency of psychiatric diagnoses.

Furthermore, the results showed different patterns of associations between exogenous hormones (hormonal contraception or HT) and mental health. Use of hormonal contraception was not associated with worse psychological status or depressive symptoms/disorders. However, the prevalence of depressive and anxiety disorders among women in connection with the menopausal transition was high, and in this group an

Table 6. Summary of the main findings.

Study	Results
Study I	• Trend for higher prevalence of MDD, more severe depressive and anxiety symptoms in women with a history of miscarriage (compared to those without such a history) • Associations between history of miscarriage and MDE and other depressive/anxiety symptoms • Associations between number of miscarriages and psychiatric diagnoses (especially depression), GHQ-12 score and other depressive/anxiety symptoms
Study II	• No association between OC use and BDI-21 or GHQ-12 score or CIDI diagnoses • Negative associations between duration of OC use and some BDI-21 items • Positive association between the duration of OC use and alcohol dependence • No effects with regard to third- vs. second-generation COCs • Negative associations between use and duration of use of the LNG-IUS and depressive symptoms (BDI-21)
Study III	• Some negative associations between OC use and depressive symptoms • No noteworthy associations between duration of use of OC and psychiatric symptoms • No noteworthy associations between LNG-IUS use or its duration and psychiatric symptoms/disorders
Study IV	• High prevalence of psychopathology among perimenopausal and postmenopausal women using HT • Associations between HT use and psychiatric diagnoses, in specific depression and anxiety disorders • Associations between HT use and depressive/anxiety symptoms

Abbreviations: Beck Depression Inventory-21 items (BDI-21), Combined Oral Contraceptive (COC), Composite International Diagnostic Interview (CIDI), General Health Questionnaire-12 items (GHQ-12), Hormone Therapy (HT), Levonorgestrel-Intrauterine System (LNG-IUS), Major Depressive Disorder (MDD), Major Depressive Episode (MDE), Oral Contraceptive (OC).

association between current HT use and worse psychological well-being or mental health has emerged.

5.2 Miscarriage and mental health (Study I)

Analyses were carried out among women aged 30 to 50 years in Health 2000 data, and 25 to 50 years in FINRISK 2002 data, separately in the age groups ≤ 40 years and 41–50 years.

Of the 1936 participants in the Health 2000 survey, 1469 had had one or more pregnancies, and 351 (23.9%) of them had had one or more miscarriages (missing data for 1). The mean number of miscarriages was 1.4 (SD 1.4; range 1–20); two of the women with a history of miscarriage had had no live births (data missing for 31) and 98 of them (27.9%) reported previous infertility.

Of the 2903 participants in the FINRISK survey, 2169 had had one or more pregnancies, and 462 (21.5%) of them had had one or more miscarriages (missing data 16). The mean number of miscarriages was 1.4 (SD 0.7; range 1–6); 22 of the women with a history of miscarriage had had no births (data missing for 12), and 133 of them (29.7%, data missing for 14) reported previous infertility.

5.2.1 History of miscarriage

In the Health 2000 dataset a trend towards higher prevalence of MDD was found among women with a history of miscarriage (9.8% vs. 7.3%, NS); also, they had higher BDI-21 score (7.3 vs. 6.1, $p<0.05$) and GHQ-12 score (2.1 vs. 1.8, $p<0.01$) when compared with women without such a history. Similarly, in the FINRISK survey the prevalence of depression and other psychological disorders tended to be higher among women with a history of miscarriage (6.8% vs. 5.8%, NS; 1.7% vs. 1.3%, NS, respectively).

After controlling for possible confounding factors in the multivariable analyses, a positive association was found between history of miscarriage vs. recent diagnosis of MDE (OR=1.830; 95% CI=1.005–1.334; $p<0.05$) only in the age group 41–50 years, and vs. several BDI-21 and GHQ-12 items only in the age group 30–40 years (BDI "impaired working capability": B=0.161, 95% CI=0.044–0.278, $p<0.01$; GHQ "strain": B=0.192, 95% CI=0.048–0.335, $p<0.01$; "impaired enjoyment": B=0.118, 95% CI=0.015–0.220, $p<0.05$; "impaired problem coping": B=0.110, 95% CI=0.022–0.199, $p<0.05$) (Health 2000). However, no associations were found with any psychiatric diagnosis in the previous year either in the Health 2000 ("any CIDI diagnosis", 30–40 year group: OR=0.895, 95% CI=0.511–1.568, $p>0.05$; 41–50 year group: OR=1.364, 95% CI=0.862–2.159, $p>0.05$) or in FINRISK ("recent diagnosis of depression", 25–40 year group: OR=0.710, 95% CI=0.455–1.109, $p>0.05$; 41–50 year group:

OR=0.999, 95% CI=0.487–2.050, p>0.05; "other recent psychiatric diagnosis", 25–40 year group: OR=3.664, 95% CI=0.865–15.516, p>0.05; 41–50 year group: OR=0.824, 95% CI=0.173–3.932, p>0.05). Additionally, only a slightly significant negative association with recent anhedonia (OR=0.614; 95% CI=0.377–0.998; p<0.05), limited to the age group 25–40 years (FINRISK 2002), was detected. However, most of the significant associations were characterized by small effect sizes.

5.2.2 Number of miscarriages

After controlling for possible confounding factors (including the reproductive status), the number of miscarriages was associated, among women aged 30–40 years in the Health 2000 study, with any current psychiatric CIDI diagnosis (OR=2.069; 95% CI=1.116–3.835; p<0.05), as well as with GHQ-12 total score (B=0.636; 95% CI=0.047–1.224; p<0.05). Moreover, associations were observable between the number of miscarriages and several items of the BDI-21 ("feeling of looking ugly": B=0.172, 95% CI=0.028–0.317, p<0.05; "tiredness": B=0.123, 95% CI=0.013–0.233; p<0.05) and GHQ-12 ("impaired concentration": B=0.112, 95% CI=0.014–0.209, p<0.05; "feelings of usefulness": B=0.096, 95% CI=0.012– 0.180, p<0.05; "loss of self-confidence": B=0.165, 95% CI=0.003–0.327, p<0.05). With regard to the age group 41–50 years, the number of miscarriages was positively associated with the BDI-21 items "crying" (B=0.098; 95% CI=0.026–0.171; p<0.01), "irritability" (B=0.167; 95% CI=0.013–0.321; p<0.05) and "feeling of looking ugly" (B=0.158; 95% CI=0.062–0.254; p<0.01), and negatively associated with the GHQ-12 item "feeling of overcoming difficulties" (B=-0.120; 95% CI=-0.233–-0.007; p<0.05).

In the analyses from FINRISK 2002, number of miscarriages resulted to be associated with a recent diagnosis of depression only among women aged 41–50 years (OR=2.689; 95% CI=1.334–5.420; p<0.01), and with report of "frightening thoughts" (B=0.173; 95% CI=0.033–0.314; p<0.05) among women aged 25–40 years.

5.3 Hormonal contraception and mental health (Studies II and III)

Studies II and III examined the possible associations between use of hormonal contraception (OC and the LNG-IUS) and duration of their use vs. mental health and psychological well-being. The data sources were Health 2000 for Study II and FINRISK 1997, 2002 and 2007 for Study III. Figures related to OC and LNG-IUS use in the two studies are reported in Figures 9 and 10.

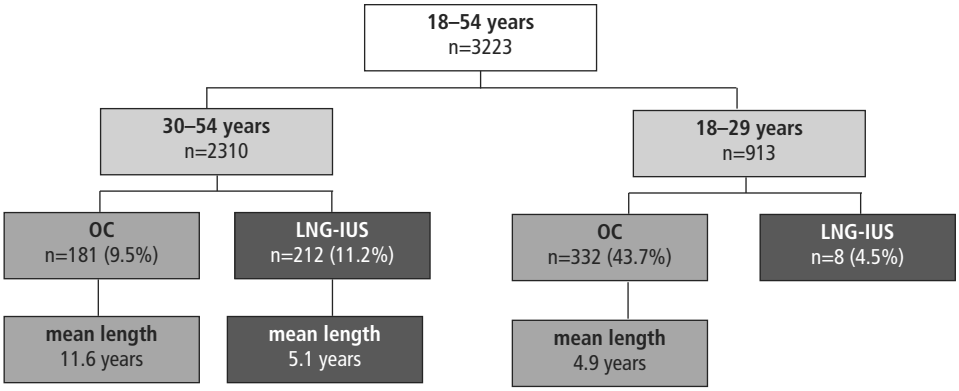
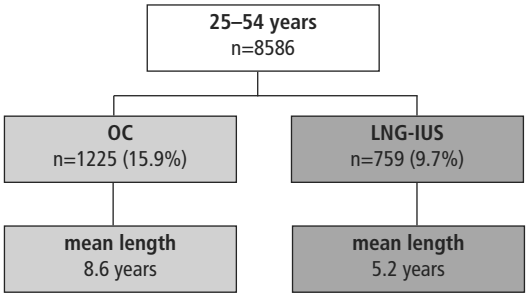


Figure 9. Use of hormonal contraception and its duration among participants in Health 2000.



Abbreviations: Levonorgestrel-Intrauterine System (LNG-IUS), Oral Contraceptive (OC).

Figure 10. Use of hormonal contraception and its duration among participants in FINRISK 1997, 2002 and 2007.

5.3.1 Oral contraceptives

Even though the prevalence of psychiatric disorders, in particular alcohol dependence (9.1% vs. 3.8%, $p<0.01$), but also MDE (10.4% vs. 7.5%, NS), MDD (9.1% vs. 7.3%, NS) and dysthymic disorder (3.6% vs. 1.7%, NS) tended to be slightly higher, a tendency for lower BDI-21 score (5.9 vs. 6.5, NS) was found in OC users than in non-users in Health 2000. Different figures were found in FINRISK, with OC users having a lower prevalence of depression (5.5% vs. 7.8%, $p<0.05$) and other psychiatric disorders (1.9% vs. 2.6%, NS), as well as less and less severe depressive symptoms (depressed mood: 23% vs. 26%, $p<0.05$; anhedonia: 19% vs. 22%, $p<0.01$; BDI-21 score: 6.8 vs. 8.4, $p<0.01$) than non-users.

In multivariable analysis OC use only associated with the BDI item "feelings of worthlessness" (Health 2000) (B=-0.127; 95% CI=-0.238–-0.015; p<0.05). No other associations were found with BDI-21 and GHQ-12 score or current psychiatric diagnosis in the Health 2000. On the contrary, OC current use was negatively associated with BDI-13 (but not BDI-21) total score (B=-0.418; 95% CI=-1.791–-0.044; p<0.05) and some BDI items ("feelings of dissatisfaction": B=-0.101, 95% CI=-0.202–-0.001, p<0.05; "feelings of worthlessness": B=-0.093, 95% CI=-0.180–-0.005, p<0.05; "irritability": B=-0.207, 95% CI=-0.368–-0.046, p<0.05; "lost interest in people": B=-0.068, 95% CI=-0.124–-0.013, p<0.05; and "lost appetite": B=-0.040, 95% CI=-0.074–-0.007, p<0.05) in analyses from FINRISK surveys.

The duration of OC use was inversely associated with some of the BDI-21 items ("feelings of dissatisfaction": B=-0.031, 95% CI=-0.052–-0.009, p<0.01; "irritability": B=-0.030, 95% CI=-0.055–-0.006, p<0.05; "lost interest in people": B=-0.016, 95% CI=-0.030– -0.002, p<0.05; "earlier waking": B=-0.029, 95% CI=-0.053–-0.005, p<0.05; and "lost interest in sex": B=-0.024, 95% CI=-0.043–-0.005, p<0.05), as well as with the diagnosis of MDD (OR=0.878; 95% CI=0.777–0.992; p<0.05), but positively related with higher risk of alcohol dependence (OR=1.485; 95% CI=1.134–1.944; p<0.01) and with more BDI-21 "worries about one's health" (B=0.017; 95% CI=0.003–0.031; p<0.05) (Health 2000). In FINRISK only a few significant associations, all characterized by small effect sizes, emerged ("anhedonia in the previous year": B=0.041, 95% CI=0.005–0.079, p<0.05; "irregular heart rate": B=0.009, 95% CI=0.001–0.018, p<0.05; and "insomnia": B=0.009, 95% CI=0.002–0.017, p<0.05).

When testing for the effects of third vs. second generation COCs on mental health and psychological well-being, a significant difference emerged only in association with the GHQ item "impaired decision-making" (B=-0.120; 95% CI=-0.209–-0.031; p<0.01).

5.3.2 The LNG-IUS

In general, psychiatric disorders and symptoms tended to be less prevalent among users of the LNG-IUS compared with non-users (Table 7).

In the multivariable analysis of the current use of the LNG-IUS and its duration, the main association was the one between LNG-IUS use and BDI-21 total score in Health 2000 (B=-0.988; 95% CI=-1.917–-0.059; p<0.05). Additional significant associations, mostly characterized by small effect sizes, were detected between current use of the LNG-IUS and the BDI-21 item "earlier waking" (B=-0.221; 95% CI=-0.356–-0.087, p<0.01) and the GHQ-12 item "impaired concentration" (B=-0.073; 95% CI=-0.145–-0.002; p<0.05) (Health 2000). No significant associations emerged in analyses from FINRISK data. The duration of the LNG-IUS use associated with the GHQ-12 item "strain" (B=-0.027; 95% CI=-0.052–-0.002; p<0.05) (Health 2000) and with the general symptom "confusion" (B=0.021; 95% CI=0.006–0.036; p<0.01) (FINRISK Surveys).

Table 7. Prevalence of psychiatric morbidity, and BDI-21, BDI-13 and GHQ-12 mean scores, among LNG-IUS users vs. nonusers.

	current LNG-IUS users	LNG-IUS non-users
	Health 2000	
Any current psychiatric diagnosis	27 (13.6%) (n=198)	278 (18.7%) (n=1489)
Alcohol abuse	0 (n=200)	10 (0.7%) (n=1520)
Alcohol dependence	6 (3.0%) (n=200)	68 (4.5%) (n=1517)
Dysthimic disorder	3 (1.5%) (n=200)	29 (1.9%) (n=1524)
MDE	9 (4.5%) (n=200)	124 (8.1%) (n=1525)
MDD	9 (4.5%) (n=200)	119 (7.8%) (n=1525)
Anxiety disorder	9 (4.5%) (n=198)	93 (6.5%) (n=1493)
BDI-21 score (mean)	5.5**	6.6
GHQ-12 score (mean)	1.6	1.8
	FINRISK	
Recent depression diagnosis	46 (8.0%) (n=576)	342 (7.3%) (n=4656)
Other psychological illness	11 (1.9%) (n=577)	117 (2.5%) (n=4649)
Depressive symptoms during the past year	184 (24.4%) (n=755)	1788 (25.5%) (n=7010)
Anhedonia during the past year	143 (18.9%) (n=757)	1550 (22.1%) (n=6998)*
BDI-21 score (mean)	8.3	8.2
BDI-13 score (mean)	0.9	1.0

* χ^2 test or t-test significant at $p<0.05$
** χ^2 test or t-test significant at $p<0.01$
Abbreviations: Beck Depression Inventory-13 items (BDI-13), Beck Depression Inventory-21 items (BDI-21), General Health Questionnaire-12 items (GHQ-12), Levonorgestrel-Intrauterine System (LNG-IUS), Major Depressive Disorder (MDD), Major Depressive Episode (MDE).

5.4 Hormone therapy and mental health (Study IV)

More than a quarter (n=406; 28.4%) of the 2640 women in the age group 40–74 years in the Health 2000 cohort, and 1464 (28.3%) of the 9449 women in the same age group from the FINRISK surveys reported having used HT during the month prior to the survey; 68 (16.7%) out of the 406 HT users in Health 2000 were perimenopausal. Descriptive analyses of HT users vs. non-users revealed a higher prevalence of psychiatric disorders (MDE and MDD: 9.8% vs. 4.2%, $p<0.001$; anxiety disorder: 8.1% vs. 4.6%, $p<0.05$) and depressive/anxiety symptoms (low mood: 26.7% vs. 21.1%, $p<0.001$; anhedonia: 23.1% vs. 19.8%, $p<0.05$; GHQ-12 mean score: 2.3 vs. 1.8, $p<0.05$) in perimenopausal and postmenopausal women currently under HT. No significant difference emerged with regards to alcohol dependence (2.3% vs. 1.8%, NS).

Current HT use was positively associated with the presence of any psychiatric diagnosis or use of any psychotropic drugs in the past 12 months (OR=1.435; 95%

CI=1.231–1.672; p<0.001), and in specific with a diagnosis of depression (Health 2000: OR=2.459, 95% CI=1.484–4.074, p<0.001; and FINRISK: OR=1.444, 95% CI=1.111–1.877, p<0.01), as well as with anxiety disorders (Health 2000: OR=2.219, 95% CI=1.319–3.732, p<0.01). Additionally, current use of HT was associated with reports of depressed mood in the past year (FINRISK: OR=1.222, 95% CI=1.040–1.437, p<0.05) and with several depressive and anxiety symptoms (general symptoms: "feeling tense and nervous": B=0.066, 95% CI=0.022–0.110, p<0.01; "frightening thoughts": B=0.046, 95% CI=0.001–0.092, p<0.05; "nightmares": B=0.049, 95% CI=0.012–0.085, p<0.01; "feelings of depression": B=0.069, 95% CI=0.024–0.113, p<0.01; and "headache": B=0.087, 95% CI=0.048–0.126, p<0.001; GHQ-12 "feelings of depression": B=0.102, 95% CI=0.007–0.197, p<0.05; GHQ-12 "unhappiness": B=0.082, 95% CI=0.015–0.150, p<0.05; and BDI-21 "loss of interest in sex": B=-0.187, 95% CI=-0.281–-0.093, p<0.001). However, most of the associations were characterized by small effect sizes.

No significant differences emerged when testing whether different preparations (estrogen-only vs. combined preparations, oral estrogens vs. parenteral estrogens, combined cyclic preparations vs. combined continuous preparations) differently influenced mental health (data not shown).

6 Discussion

In general, the results of this research are suggestive of a relationship between mental health and reproductive health in women. Given the large sample size of the two population-based studies employed in this investigation (Health 2000 and FINRISK Surveys), and the consequent good generalization of the results, the findings provide a valuable contribution to the research in the field. However, the original hypotheses were not all completely proved.

6.1 Main findings

The key findings are those of an association between miscarriage as a pregnancy outcome, as well as the use of exogenous hormones (hormonal contraception or HT), and women's psychological well-being or mental health.

In detail, a history of miscarriage as well as the number of miscarriages were found to be associated with adverse outcomes in terms of psychological well-being or mental health. Also, a high prevalence of depressive and anxiety disorders in connection with the menopausal transition was detected. While the current use of HT was associated with worse psychological well-being or mental health, the use of hormonal contraception seemed not to relate to depressive symptoms or disorders or to other adverse psychological conditions.

6.2 Strengths and limitations

The main strength of this study is the use of nationwide, population-based samples, with a relatively good response rate: these factors allow a good generalization of the results. Also, the use of different diagnostic tools—mostly of proven high validity and reliability—to assess mental health, provides a guarantee that the results were not due to the properties of any single instrument.

However, the study has some limitations. The first stems from the cross-sectional, partially retrospective design of the surveys. This precludes any causal relationship between the studied variables. Additionally, the use of different instruments to assess mental health in some cases precluded any reliable comparison of the results gained from the Health 2000 and FINRISK Surveys. In particular, mental health was better and more specifically assessed in the Health 2000 study.

Another limitation arises from the self-reported quality of the mood and psychological well-being assessment both in the Health 2000 and FINRISK studies. Nevertheless, the validity and reliability of the BDI-21, BDI-13 and GHQ-12 scales have

been widely demonstrated (Goldberg et al., 1976; Beck et al., 1988). Furthermore, in Health 2000, a structured interview with established validity and reliability (Wittchen et al., 1998), and administered by trained interviewers, was used to assess the presence of current psychiatric diagnoses. In the FINRISK Survey, mental health was assessed mostly via self-reported questions rather than through structured interviews or clinical evaluations. However, even though self-reported psychiatric symptoms and diagnoses may be biased by patients' attitude or misperception, a good agreement has previously been reported (DeFife et al., 2010; Kelly et al., 2011) between the symptoms and levels of functioning reported by the patients and clinical evaluations, as well as clinical concept and definition of depression (and the criteria commonly included in the diagnostic tools).

Perhaps the main limitation is due to the fact that almost all the studied groups (OC-, LNG-IUS- and HT- users vs. non-users) were constituted by choice rather than chance. Therefore, it is plausible that the results were influenced by factors involved in deciding on hormonal contraception/HT use (mostly dependent on women's own decision or that of the health care provider). Even though most of the findings were controlled for, several other factors may have biased the results.

Lastly, many of the significant associations detected in the analyses were accompanied by small effect sizes, probably as a consequence of the large sample size.

6.3 Miscarriage and mental health (Study I)

6.3.1 History of miscarriage

Results from the first study showed that a history of miscarriage is associated with depressive and anxiety symptoms in women aged 30 to 50 years.

A miscarriage is known to be a stressful event for a woman, and it may be followed by a grief reaction resembling the one occurring after the death of a loved one (Brier, 2008; Adolfsson & Larsson, 2010; Kersting & Wagner, 2012). In fact, a miscarriage is a true experience of loss. Additionally, it is characterized by its own features, since there is no possibility for concrete memories of the loved one: thus, the image of the loved one relies mostly on the mother's mental representation and dreams (Brier, 2008).

The literature studying the possible mental health outcomes of a miscarriage has been broad, with quite inconsistent findings. Beutel et al. (1995) reported that the majority of the symptoms detected in the short-time following a miscarriage (mostly depressive and anxiety-related) were gradually attenuated at the six- and 12-month follow-ups (even though remaining more severe than in the general population). However, a subgroup of women developed a depressive (or grief-depressive) reaction (rather than a pure grief reaction), and they seemed to be at risk of a long-term depressive status. Recently, in their longitudinal studies, Lok et al. (2010) and Sham et al. (2010) showed low psychological well-being and high levels of psychopathology (new

onset or recurrent psychiatric, especially depressive, disorders or symptoms) in women in the short term after a miscarriage. With regard to the duration of the symptomatic reaction following a miscarriage, most of the literature is consistent in claiming that it is normally self-limiting, and the symptoms subside within six to 12 months after the event (Nikcevic et al., 1999; Broen et al., 2005; Brier, 2008). However, it seems that some, more vulnerable women can be at higher risk of psychological distress, especially on the depressive side, even in the long term, and Lok et al. (2010) found that initially more distressed women had persisting elevated depressive symptoms, even at one year post-miscarriage. Moreover, young women experiencing a pregnancy loss, be it miscarriage or induced abortion, seem to have an increased risk of lifetime alcohol and substance use disorders and a higher risk of affective disorders when compared with women who had a live birth (Dingle et al., 2008).

The current study partly supports the hypothesis of a subgroup of more vulnerable women who are at higher risk of psychiatric consequences even in the long term after the pregnancy loss. This is perhaps one of the first studies to analyze the relationship between miscarriage and mental health using two large, population-based datasets, with detailed background information. Furthermore, it was possible to combine the data from the two studies, resulting in an extremely large sample, highly representative of the Finnish population. In addition, while most of the research has generally focused on the short-term effects of a miscarriage (or other pregnancy losses), the possible long-term outcomes were also considered in the current work. However, it must be remembered that this was a cross-sectional study with retrospective data collection. Therefore, no causal conclusion can be drawn. This is especially true since no information concerning the time when the miscarriage occurred or the onset of the psychiatric disorder/symptoms was available. Similarly, the social and psychological conditions at the time of the miscarriage or in the immediate aftermath were also unknown. These factors are recognized as influencing the reaction to a miscarriage, since the presence of marital and social support may help the grief process, while certain personality traits (e.g., neuroticism) and previous psychopathology (e.g., previous depressive episodes) may increase the risk of a complicated and long-lasting reaction to the pregnancy loss. In addition to this, it warrants a mention that a range of life events, which possibly occurred in the time span between the index event and the current evaluation, could rather explain the current findings. In order to partially limit this potential bias, the study population was limited to women aged 30 (Health 2000) or 25 (FINRISK) to 50 years; moreover, separate analyses were conducted in two different age groups (≤ 40 years and 41–50 years). Different reactions to a past pregnancy loss were expected, given that these two groups were in different phases of their reproductive lives. In fact, when looking at the main depressive symptoms and diagnoses, it seems that there was no significant relationship with a history of miscarriage either in younger or older women, with an increased risk of MDE only in women aged 41 to 50 years. However, when looking at single item analyses, a number of associations, mostly indicative of a functional impairment as a consequence of a miscarriage, were evident

in the young group, though not among women older than 40 years. This could be explained by the different (psychological and physical) meaning that a pregnancy (and a pregnancy loss) may have in fertile aged women and in women approaching the menopausal transition. Even though all the analyses controlled for the reproductive status and for the number of (live) births, still it is possible that different patterns of associations in the two age-groups are an expression of the overall different reproductive states of the group themselves.

6.3.2 Number of miscarriages

The results of this research also suggest that additional miscarriages may be associated with increasing severity of psychological impairment. This is in contrast with the results presented by some authors (Klier et al., 2000; Adolfsson & Larsson, 2010; Sham et al., 2010), who have found no increased risk of depressive reaction or other psychiatric symptoms in the case of a further miscarriage. Also, women presenting with high vs. low GHQ-12 and BDI-21 scores after a miscarriage seemed not to differ in terms of their obstetric history (i.e. previous miscarriages, previous induced abortions, history of infertility and planned pregnancy) (Lok et al., 2010). However, some older studies (Friedman & Gath, 1989; Thapar & Thapar, 1992; Janssen et al., 1996) have shown more depressiveness and/or anxiety in women with a history of previous miscarriages. Women with a history of recurrent pregnancy losses were also found to have poorer quality of life and more depressive and anxiety symptoms during a subsequent pregnancy than pregnant women with no history of pregnancy loss (Couto et al., 2009). In contrast to previous research, the current study specifically focused on the association between the number of miscarriages (as a linear variable) and mental health status.

In this study, when looking at the single-item analyses, most of the significant items were those indicating self-criticalness (i.e., uselessness, negative self-view, loss of self-confidence), which in turn might lead to beliefs and feelings of (biological) inadequacy. Interestingly, these associations were detected in both age groups (even though they were more evident in young women), and irrespectively of reproductive status. This finding might have some clinical implications. Indeed, the theme of self-criticalness and self-blame in relation to the cause of the miscarriage, especially when unknown, is frequently raised after a spontaneous pregnancy loss (Stratton & Lloyd, 2008; Kersting & Wagner, 2012). Therefore, it could be hypothesized that a (psycho-) therapeutic approach to miscarrying women, especially those having multiple pregnancy losses, should address the question of self-inadequacy, self-criticalness and self-blame, together with a revision of the causes of the miscarriage.

Even though there are several limitations, these results emphasize the importance of assessing psychological well-being when counseling women with a history of miscarriage, as well as of inquiring into reproductive history when assessing psychopathology in women.

6.4 Hormonal contraception and mental health (Studies II and III)

The results of Studies II and III showed no associations in terms of negative effects of hormonal contraception on mental health. Rather, they are suggestive of a potential beneficial influence of OCs, and in particular from long duration of use, on mood.

There is still quite a debate on the beneficial and potentially harmful side effects of hormonal contraception in relation to mental health, especially mood and anxiety symptoms/disorders. Even though some of the most recent studies did not find any influence of oral contraceptives in respect to mood (especially depressive) swings (Duke et al., 2007; O'Connell et al., 2007), nevertheless depression and depressiveness as well as mood changes in general are a common complaint among OC users, as well as a common reason for OC discontinuation (Oinonen & Mazmanian, 2002).

6.4.1 Oral contraceptives

Women currently taking OCs tended to have a lower prevalence and less severe depressive symptoms in comparison with women who were not taking them. No significant associations were detected with most of the BDI-21 and BDI-13 items, or with the risk of any psychiatric diagnosis. It could thus be concluded that current OC use has no significant detrimental effect on mood. By contrast, it may have some favorable effects. However, being again a cross-sectional, partly retrospective study, no temporal and causal relationship between the studied variables can be established. Indeed, there was no information on the timing of onset of possible psychiatric disorders/symptoms. Additionally, a possible "healthy survivor effect" could not be excluded, i.e. that some of the non-OC users, with apparently more psychological distress, were past users that discontinued OCs because of side effects, including mood side effects. This would be in line with some literature reports showing that those women who develop mood side effects from OCs are those same women who are at increased risk of other hormone-related psychiatric disorders, such as postpartum (Bloch et al., 2005) and perimenopausal depression (Stewart & Boydell, 1993). Additionally, women vulnerable to mood swings in association with OC seem to have specific "predisposing" personality traits (somatic anxiety, stress susceptibility) (Borgström et al., 2008). These results are all suggestive of a vulnerability to emotional side effects of OCs, where the vulnerability could be due to an increased hormonal sensitivity and/or due to specific personality traits.

Interestingly, the results of the current study did not change when testing for the possible influence of third- vs. second-generation COCs. This is of particular interest, since most of the research on this topic has thus far focused on a specific COC compound, or compared COCs with progestin-only pills or placebo (Böttcher et al., 2012), rather than on different generations of COCs. However, as noted by Böttcher et al.

(2012), the progestogenic component of the COCs, as well as the dose of the estrogenic component, has rapidly changed in the recent decades, leading to possibly more effective and better tolerated preparations. Indeed, from the available literature it seems that second-generation COCs, with more androgenic characteristics, have a worse impact on mood than third-generation preparations (Poromaa & Segebladh, 2012).

6.4.2 The LNG-IUS

Similar results were gained in respect to the LNG-IUS. To the best of my knowledge, this is the first study in which the relationship between mental health and use of the LNG-IUS has been directly addressed. To date, the research has mainly focused on satisfaction rates and on the effectiveness of the LNG-IUS, mostly examining its possible side effects in general terms. However, even though the circulating concentrations of levonorgestrel are low in women using the LNG-IUS, the hormone released is rapidly absorbed into the systemic circulation and is detectable in plasma 15 minutes after insertion of the device (Luukkainen, 1991). It would have therefore not been surprising if some women had experienced hormonal side effects, including the psychological ones. Indeed, even though most of the studies report good effectiveness and high satisfaction rates (around 90%) among LNG-IUS users and with improved quality of life and psychological well-being (Skrzypulec & Drosdzol, 2008), some investigators have nevertheless reported only a 50% rate of satisfaction, with the most commonly reported reasons for discontinuation being bleeding, progestogenic adverse effects and abdominal pain (Daud and Ewies, 2008; Ewies, 2009). Similarly, in a Finnish survey on premature removal of the LNG-IUS, pelvic infections, pain, depression and recurrent vaginal infections were reported as rather uncommon reasons for discontinuation (Backman et al., 2000). However, the findings from Studies II and III show that women currently using the LNG-IUS are not more depressed or in a worse psychological condition than women not using it, suggesting that the LNG-IUS *per se* has a minimal effect, if any, on mental health.

6.4.3 Duration of use of hormonal contraception

To date, only a few studies have been carried out on large samples and on a population basis to specifically investigate the influence of the duration of hormonal contraception use (Duke et al., 2007; Ryan et al., 2008), in particular of the LNG-IUS, on mental health.

From the current research, it could be inferred that long term use of contraception, be it OC or the LNG-IUS, was not associated with increasing severity of psychological, especially depressive, symptoms or disorders. Rather, it seems that the longer the duration of current use of OCs is, the lower the scores in connection with many BDI-21 items, and the lower the risks of MDD are, in line with the findings of Duke

et al. (2007). Again these results could partly be an expression of a "healthy survivor effect", with women experiencing no side effects being more likely to continue using the same preparation for a longer time. Nevertheless, a further important implication would be that those women who have encountered no psychological side effects in the early stages of use of hormonal contraception are not likely to develop them later during their use. This consideration needs to be further tested in longitudinal prospective studies.

The only exception to this pattern was the association between the duration of current OC use and alcohol dependence. The question of the possible influence of sex steroids in general and hormonal contraceptives in particular on ethanol metabolism is still controversial (Warnet et al., 1984; King & Hunter, 2005). The findings of this study could be the result of possibly related confounding (e.g. psychosocial) factors. Indeed, it is possible that women with lifestyle factors associated with alcohol dependence (e.g. risky sexual behavior or multiple partners) have been using (or have been advised to use) an effective contraceptive method (e.g. an OC) for a relatively long time. Also, because of the cross-sectional design of the study, the possibility that women with mental health problems or alcohol dependence have themselves chosen or have been advised to use the most effective methods of contraception (i.e. OCs and the LNG-IUS) for a long time, cannot be ruled out.

6.5 Hormone therapy in perimenopausal and postmenopausal women (Study IV)

The findings from study IV did not support the original hypothesis of better psychological well-being or mood in HT users, in particular in those using estrogen-only preparations. Indeed, a high prevalence of psychiatric disorders and symptoms, in particular depressive and anxiety ones, was found among HT users. Also, after controlling for potential confounding factors in the regression analyses, an association between current use of HT and psychiatric morbidity was detected. These findings contrast with most of the literature on this issue. Indeed ET has been shown to be effective in alleviating depressive symptoms related to the menopausal transition, and it has been suggested as a therapeutic option, alone or as part of an augmentation strategy, for the treatment of perimenopausal depression. However, it warrants notice that only a combination of estrogen plus progestogens can be administered in women with an intact uterus, given the increased risk of endometrial hyperplasia in the case of unopposed estrogen administration (The Writing Group for the PEPI Trial, 1996). The effects of progestogens on mood are quite questionable, and it seems that they may counteract the positive estrogenic effects and even induce depressive mood swings (Sherwin, 1999). Studies show that postmenopausal healthy women experience a worsening of mood during the estrogen-progestogen phase of their EPT cy-

cles when compared with the estrogen-only phase (Björn et al., 2000). It is therefore possible that the progestogenic component of EPT may account for some psychological side effects in a subgroup of women. Other studies have confirmed the hypothesis that different hormone combinations may exert different effects on mood and anxiety (Cagnacci et al., 2004), suggesting that the choice of whether to use estrogen alone or a combination of estrogen plus progestogen, and in the latter case, which progestin, has to be carefully evaluated and adapted to the individual subject (Björn et al., 2000; Cagnacci et al., 2004). Additionally, past (but not current) use of HT was found to be associated with an increased risk of depression in elderly community-dwelling women, when compared with never-users (Ryan et al., 2008). However, Ryan et al.'s study did not take into account the effect of different HT compounds. A second study by the same research group and carried out on the same population found no association between (current or past) use of HT and anxiety disorders, irrespectively of the HT compounds (Scali et al., 2009). In Study IV it was partly possible to control for the effects of different HT compounds and different routes of administration. However, this control was limited to a subset of the original sample, since this information was not available with respect to FINRISK 1997 and 2002, i.e., in the oldest datasets, where the use of older preparations is more likely.

The results of Study IV may also reflect the fact that HT users are probably a selected population of women with more severe somatic and/or psychiatric illnesses, as well as with more disturbing climacteric symptoms. It could be speculated that these subjects are more prone to seek clinical help and have more contacts with the health care system, and are therefore more likely to be prescribed HT (Wilson et al., 1998; Bardel et al., 2002), as well as to have a psychiatric disorder detected and diagnosed by a clinician. In contrast, "healthier" women, with fewer climacteric complaints, probably see health professionals more seldom, and are therefore not prescribed HT.

Hence, even though these results do not allow establishing any causal and/or temporal relationship between use of HT and recent psychological status, they highlight the high prevalence of psychiatric morbidity (either in terms of depressive and anxiety symptoms or disorders) in the perimenopausal and postmenopausal population. Also, on the basis of these findings, using HT only for treating perimenopausal depression could not be recommended.

6.6 Clinical implications and future research

This study shows a close and multifaceted relationship between mental status and the reproductive life of women. Perhaps the main clinical correlate of these findings is once more the importance of considering gender-specific and individual approaches when assessing mental status and treating patients in general. Indeed, it is clear how psychological well-being and psychopathology, but also life events, including reproductive events, and their perception differ between genders as well as inter-individually.

In particular, the results of this study highlight the importance of considering reproductive health and events when assessing psychological status and mental health in women. A history of miscarriage, especially of recurrent miscarriage, should be inquired into. Reciprocally, psychological well-being should be assessed when counseling women with a history of miscarriage. As suggested by the results from single-item analyses, the theme of self-criticalness and self-blame should be addressed during any (psycho-) therapeutic support to women following a miscarriage. Such programs should address the question of self-inadequacy, self-criticalness and self-blame, together with a revision of the causes of the miscarriage. Indeed, studies have found that, irrespective of the kind of treatment received, the amelioration of self-blame symptoms was more evident when a clear cause for the miscarriage was found (Nikcevic et al., 2007), and it is likely that awareness of the real causes of the miscarriage (including severe chromosomal aberrations, gene mutations, structural defects) may itself help in mitigating the reaction to a pregnancy loss.

Further clinical implications concern the users of hormonal contraception, who are often concerned with the possibility of mood side effects. Even though detrimental mood effects cannot be completely ruled out, nevertheless women could be reassured that only a minority of OC and LNG-IUS users are at risk of developing those mood side effects. This information should be provided to women willing to start or change their contraceptive method. Furthermore, the results showing no detrimental associations between mental health and duration of use of hormonal contraception may indirectly suggest that the onset of mood or other psychological side effects is less likely in the long-term use of hormonal contraception. This hypothesis warrants further investigation in longitudinal prospective studies.

Lastly, the importance of considering the risk of depressive symptoms and disorders in women entering the menopausal transition warrants further mention; in this group of women, on the basis of the results of Study IV, the use of HT alone for treating depressive and anxiety disorders cannot be recommended.

As this is a cross-sectional study which does not allow for drawing any causal conclusion, longitudinal studies are warranted to better study the relationship between mental health and reproductive health. In this respect, a currently ongoing study is aimed at further evaluating the relationship between contraceptive use and mental health in terms of alcohol and substance use, sleep disturbances, depressive and anxious symptoms, deliberate self-harm and suicidal ideation and suicide attempts. The study participants are women aged 18 years or over who attend a gynecological (family planning) examination in order to start contraception or, if already using contraception, to attend an ordinary check-up. Attention will be focused on the type and composition of contraceptives as well.

In addition to this, future research could focus on the associations between mental health and other reproduction-related variables. There is still quite a debate concerning the possible influence of an induced abortion on mental health. A future study could focus on this issue by analyzing the data of the 913 young women (aged 18 to

29 years) who participated in the Health 2000 survey, and in particular of the young women who participated in the Mental Health in Early Adulthood in Finland study. Moreover, data from the follow-up study Health 2011 could be considered in the analyses. Additional data concerning reproductive events, pregnancy outcomes and hospitalizations could be gained through a linkage to the Medical Birth Register (number and outcome of births), the Abortion Register (induced abortions in hospital register) and the records on spontaneous abortions treated in hospitals and in specialized health care.

7 Conclusions

On the basis of these results, the questions asked previously could be answered.

I. *Is a history of miscarriage related to further impairment of mood or psychological well-being? If so, is this impairment related to the increasing number of miscarriages?*
Associations were found between history of miscarriage and depressive and anxiety symptoms and disorders. In addition, the results show an increasing risk for psychopathology with increasing numbers of miscarriages. Therefore, the original hypothesis was supported by the results.

II. *Does hormonal contraception have any influence on mental health or psychological well-being? Do different hormonal compounds differently influence mental health? Is the duration of use of hormonal contraception related to mental health?*
Hormonal contraception, either OC or the LNG-IUS, does not have any detrimental influence on women's mental health or psychological well-being; rather, it can have some beneficial influence. However, there seems to be no difference between different hormonal compounds (third- vs. second-generation pills). The effect of the duration of contraceptive use on mental health is less clear. However, again it seems that long duration of use is not related to any detrimental, but rather a beneficial, influence on psychological status. Therefore, the original hypotheses were supported by these results where the effects of use and duration of contraception are concerned; it was not proven in respect to the effects of different hormonal contraceptives.

III. *Does hormone therapy in perimenopausal and postmenopausal women have any influence on mental health or psychological well-being? Does the relationship, if any, differ accordingly to different hormonal compounds?*
Hormone therapy in perimenopausal and postmenopausal women is not related to improved mental health; rather, it is associated with depressive and anxiety disorders, irrespective of the hormonal compounds or routes of administration. Therefore, the original hypothesis was not proven.

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