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ORIGINAL ARTICLE

Prolactin and hostility in hospitalised patients and healthy women: A systematic review and meta-analysis

J. A. Barry[1], E. Moran[2], M. Thomas[3] & P. J. Hardiman[1]

[1]*Institute for Women's Health, University College London Medical School, London, UK,* [2]*Department of Neurology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA, and* [3]*Department of Clinical Biochemistry, Royal Free London Hospital, London, UK*

The aim of this systematic review and meta-analysis was to assess any difference in the self-ratings of hostility in mentally healthy women with different levels of prolactin (PRL). Electronic databases (PubMed, MEDLINE, EMBASE and the Cochrane Library) were searched up to 2nd July 2012 for published literature comparing hostility levels in women with different levels of PRL. Keyword pairs ('prolactin' and 'aggression', 'prolactin' and 'hostil*', 'prolactin' and 'anger', and 'prolactin' and 'angry') were entered simultaneously. From 1065 resulting titles, and one unpublished study, 214 articles underwent full-text review by authors JB and EM. Studies were selected based on clinical relevance. Eight comparative studies consisting of 242 female patients with high PRL levels, 207 female patients with normal PRL levels and 127 healthy controls with normal PRL levels were included. Data were analysed using the inverse variance method with a random-effects model. Analysis revealed significantly higher hostility in patients with high PRL compared with that in healthy control women ($Z = 1.94$, $p < 0.05$; Hedges' $g = 0.72$; 95% confidence interval [CI]: −0.01–1.45), significantly higher hostility in patient controls compared with that in healthy controls ($Z = 1.94$, $p < 0.05$; Hedges' $g = 0.47$; 95% CI: 0.00–0.94) and non-significantly higher hostility levels in patients with high PRL compared with that in patients with normal PRL levels ($Z = 1.45$, $p < 0.15$; Hedges' $g = 0.38$; 95% CI: −0.13–0.89). In this meta-analysis, hostility appears to be accounted for partly by PRL levels and also partly by patient status, perhaps due to the stress of being a patient. Methodological considerations and implications for patient care are discussed.

Keywords: Hostility, meta-analysis, prolactin, patient care, review

Prolactin, pregnancy and hostility

Prolactin (PRL) receptors are seen mainly in the hypothalamus, where binding is especially high in females (Di Carlo et al. 1992). It is well established that the hypothalamus is implicated in the control of aggression in humans (Siegel and Victoroff 2009). Therefore it is plausible that PRL could be associated with aggression, especially in women around the time of birth when PRL levels are naturally at their highest (Battin et al. 1985). However, not all studies have found that PRL levels are related to hostility or aggression (e.g., Barry et al. 2014). This might be due in part to the heterogeneity of participant characteristics across the various studies, as discussed below.

PRL is not only elevated post-partum, but is elevated by other factors too. Besides a sex difference-PRL levels are roughly one-third higher in women than in men (New et al. 2004)-factors such as pregnancy, primary hyperthyroidism, medications, tumour of the pituitary, stress, anxiety and pain are all related to increased PRL levels (Mah and Webster 2002). Up to 10% of the population may have PRL levels above the normal range (Josimovich et al. 1987). Furthermore, PRL serves multiple functions in the body other than lactation. For example, PRL impacts immune function, reproductive behaviour, sleep and the stress response (Freeman et al. 2000).

Some research has found that PRL is associated with aggression in animals (Numan 1988) and hostility in humans (Fava et al. 1981; Fava et al. 1988; Mastrogiacomo et al. 1982; Kellner et al. 1984). It has been suggested that underlying this association is an adaptive mechanism called 'maternal aggression'; the high levels of PRL normally seen in female mammals shortly after giving birth promote behaviour in the mother that is protective of the newborn (Numan 1988).

Medical conditions and medication

PRL is a pituitary hormone, and hyperprolactinaemia – serum levels above 500 mIU/L – is the most common endocrine disorder of the hypothalamic–pituitary axis (Mah and Webster 2002). Pituitary tumour, a micro-adenoma that secretes PRL, is the most common cause of hyperprolactinaemia once other causes (pregnancy, primary hypothyroidism and drugs) are excluded (Mah and Webster 2002). PRL negatively regulates pituitary hormones implicated in gonadal function, thus hyperprolactinaemia is often associated with menstrual and fertility problems (Serri et al. 2003). As dopamine is a major PRL inhibitory factor, medications that impact the hypothalamic dopamine system or pituitary dopamine receptors affect PRL levels (Mah and Webster 2002). For example, tricyclic anti-depressants, opiates and other medications that affect central dopamine transmission in turn increase PRL levels (Mah and Webster 2002; Torre and Falorni 2007). Some other medications are said to increase PRL level, for example, oral contraceptives (Torre and Falorni 2007) or second-generation anti-psychotics (Penzner et al. 2009), but the effects of these medications on PRL levels may be weak.

Life stress, anxiety and pain

Patients with hyperprolactinaemia have been found to report significantly higher life event scores, when controlling for age, sex, marital status and social class (Sonino et al. 2004).

Correspondence: John A. Barry, PhD, MSc, BA, Institute for Women's Health, University College London, Pond St, London NW3 2PF, UK. Tel. + 44 207 794 0500 ext. 34081. Fax. + 44 207 830 2261. E-mail: john.barry@ucl.ac.uk

Furthermore, the onset of symptoms of hyperprolactinaemia may coincide with important life events (Nunes et al. 1980). There is evidence that stressful early life events are related to hyperprolactinaemia (Nunes et al. 1980). However, the exact role of life events in the pathogenesis of hyperprolactinaemia remains unknown (Sonino et al. 2004). The relationship may be complex; for example, although one study found that childhood stress was related to hyperprolactinaemia in adulthood, the onset of the condition did not coincide with important life events (Assies et al. 1992).

Higher PRL levels have been associated with acute stress among healthy populations (Fava and Guaraldi 1987; Biondi and Picardi 1999). It is also well established that PRL secretion is affected by stress (Freeman et al. 2000), and PRL secretion increases in response to stress in both animals (Donner et al. 2007; Torner and Neumann 2002; Torner et al. 2004) and humans (Reavley et al. 1997; Sonino et al. 2004). Anxiety is known to be related to increased PRL levels (Fava et al. 1981; Fava et al. 1988; Mastrogiacomo et al. 1982; Kellner et al. 1984; Reavley et al. 1997). Among women who are seeking medical treatment, high anxiety has been related to high levels of PRL (Fava et al. 1988; Reavley et al. 1997). Additionally, PRL is known to increase in response to pain, mediated by several neurological factors, notably dopamine levels (Ben-Jonathan and Hnasko 2001; Del Pozo and Brownell 1979).

Animal studies have shown that PRL, released in response to stress (Torner et al. 2004), decreases the stress response across a variety of dimensions (Donner et al. 2007; Torner and Neumann 2002). PRL impacts the behavioural, neurological and endocrine stress responses, for example, by decreasing stress-induced adrenocorticotropic hormone release (Donner et al. 2007; Torner and Neumann 2002).

Aggression and hostility

Research assessing PRL and aggression-related emotions generally tends to focus on hostility, rather than anger or aggression. Although anger, aggression and hostility are all similar negative emotional states and may be used interchangeably in everyday conversation, these three constructs can be distinguished from each another. Miller et al. (Miller et al. 1996) define anger as an unpleasant emotion which may be experienced cognitively and/or physiologically; aggression is an overt behaviour, which may be expressed verbally or physically; and hostility is a negative cognitive state, involving beliefs and attitudes about other people, characterised by mistrust, cynicism and suspicion of others. Also, a distinction is often made between transient states of anger and enduring trait of hostility. While state anger is evident at a particular time, trait hostility is a more enduring characteristic. It is also possible that acute levels of state anger may increase PRL levels, and the experience of a chronic stressor – such as an illness – may lead to chronic increases in PRL. High levels of hostility are furthermore related to poor physical health, especially coronary heart disease (Miller et al. 1996). In a meta-analysis assessing hostility and physical health, Miller and colleagues (Miller et al. 1996) found hostility to be an independent risk factor for coronary heart disease.

Comparability of assays over time

When comparing PRL levels over time, as in the present study where PRL samples spanning three decades are compared, it should be noted that there have been three separate International Reference Preparations (IRPs) between 1978 and 1988, each requiring a review of reference ranges for PRL (Schulster et al. 1989). Thus, the IRPs have changed from the first review in 1978 (IRP 75/504), the second in 1986 (IRP 83/562) to the third in 1988 (IRP 84/500). The assignment of unitage to the second and third IRPs has been carefully calibrated to ensure that continuity from the first IRP would be maintained. Therefore, the longitudinal application of the reference range over time can be considered robust, provided that assay kit manufacturers have appropriately recalibrated their assay against the relevant contemporary IRP.

The stability of an assay over time will also depend on other factors such as continuity of antibody, which could reduce comparability of observed values across time. However, it would be reasonable to compare broad categories of measurement over time, for example, if a value is categorised as below the norm in the 1980s then it would be reasonable to infer that it would be categorised below the norm today.

Hypothesis

Given the existing evidence on this topic, it was hypothesised that published research would find higher hostility ratings in women with elevated PRL levels.

Methods

Sources

This review followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for systematic reviews of observational studies (Stroup and Berlin 2000). A protocol for the review has been registered in PROSPERO (Centre for Reviews and Dissemination registration number: CRD42012002527).

Literature search

Articles in any language measuring hostility or aggression and PRL, which were listed in PubMed and MEDLINE published up to 2nd July 2012, and EMBASE from 1980 to 2nd July 2012, were identified. The Cochrane Review Database was also searched up to 2nd July 2012. The keyword search term pairs 'prolactin' and 'aggression', 'prolactin' and 'hostil*', 'prolactin' and 'anger', and 'prolactin' and 'angry' were entered simultaneously. The PubMed searches produced 209 articles for aggression, 65 for hostil*, 21 for anger and 24 for angry. A MEDLINE search from 1946 did not find any articles in addition to those cited in PubMed. The EMBASE searches produced 322 articles for aggression, 80 for hostil*, 43 for anger and 5 for angry. The 'related article' function was used to widen the results. The Cochrane Review Database did not produce any published reviews on PRL and aggression, hostility or anger. No further articles were produced by a hand search of relevant articles referenced in these publications. A study relevant to this topic conducted by the present authors (Barry et al. 2014) was included. Qualified librarians assisted when articles were difficult to access.

Study selection

Each article was assessed by EM or JB, and articles that fitted the main criteria (measuring PRL and aggression, hostility or anger) were accessed. When it was unclear whether an article met the inclusion criteria, an attempt was made to contact the authors. For example, the standard deviation (SD) scores for hostility in one of the studies (Groër 2005) were not presented in the published article, but an email was sent to the lead author who subsequently supplied this information. Although some studies did not report PRL values, but rather referred to groups as having 'high' or 'low' PRL levels, such studies were included as their exclusion would have limited the number of articles included in this review. Age was reported in the selected studies, but was not a factor that could be controlled for using meta-analysis because the original studies did not report outcomes by age group.

Methodological quality was independently assessed by JB and EM based on the criteria of the Newcastle–Ottawa Quality Assessment Scale (NOS) for case–control studies (Wells et al. 2000) adapted for observational studies and for the present study. In order for the methodological quality to be relevant to the present study rather than to a generalised notion of observational studies (Stang 2010), several adaptations to the criteria were made. For example, 'ascertainment of exposure' was changed to 'ascertainment of diagnosis', and studies of hospitalised patients that used other patients as controls were considered of higher quality than those that used healthy women as a control group. Other changes to the NOS criteria are listed in Table I.

Inclusion and exclusion criteria

Studies were included if they had the following features:

a) Participants were mentally healthy women, indicated by the absence of a psychiatric diagnosis.
b) Participants were grouped based on naturally occurring (rather than experimentally induced) PRL level, and hostility was the dependent (or outcome) variable.
c) Hostility was measured as a quantitative outcome using a validated questionnaire scale or subscale.
d) Hostility and PRL were reported in units of means and SDs, or were presented clearly in graphic form (e.g., a line graph with error bars, in which means and SDs could be clearly identified).
e) The studies reported other relevant data, for example, participant age, numbers of participants per group, etc.

Studies were excluded if they

a) Had mixed groups of men and women;
b) Participants were children or adolescents—these were excluded because PRL is known to act differently in children than in adults;
c) Data duplicated previously published findings.

Articles with titles or abstracts that indicated that they were not relevant (e.g., reviews, single-case studies, etc.) were excluded.

Statistical analysis

Statistical analyses were performed using Review Manager, Version 5.1. Groups of studies were meta-analysed using the inverse variance method, with a random-effects model, where there was significant heterogeneity. Heterogeneity was assessed using I^2 and chi-square statistics. An I^2 value of 30% was considered the threshold for moderate heterogeneity, and a chi-square p value < 0.10 was considered the threshold for significant heterogeneity. Thus, analyses showing I^2 values $> 30\%$ and chi-square p values < 0.10 could be analysed using a random-effects model, and heterogeneity below the thresholds

Table I. Characteristics of studies of PRL and hostility indicates (a) high PRL group, (b) patient controls and (c) healthy controls.

Study	Age (years)	N	Diagnosis/ Characteristics	Assay	Variables controlled	Time of blood sample	Hostility measure
Fava et al. (1981)	(a) 27.3 (8.2) (b) 21.4 (4.0) (c) nr	(a) 10 (b) 10 (c) 10	(a) hyperprolactinaemic amenorrhoea (b) amenorrhoea, normal PRL (c) female hospital employees	RIA	(a) & (b) no meds, age, SEC, marriage, education (a) & (b) & (c) age, SEC	(a) & (b) (8 am) (c) nr	KSQ
Mastrogiacomo et al. (1982)	(a) nr* (b) nr (c) nr *same as Fava 81	(a) 10 (b) 10 (c) 10	(a) hyperprolactinaemic amenorrhoea (b) post-partum controls (c) female hospital employees	RIA	(a) & (b) & (c) SEC[a]	(a) & (b) (8 am) (c) nr	KSQ
Kellner et al. (1984)	(a) 27.5 (3.6) (b) 35.0 (13.7) (c) 35.2 (13.2)	(a) 14 (b) 29 (c) 26	(a) hyperprolactinaemia (b) family practice patients (c) non-patient female employees	nr	(a) & (b) age, SEC, & (c) age	(a) (7–9 am) (b) & (c) nr	KSQ
Fava et al. (1988)	(a) 51.1 (13.7) (b) 47.3 (12.1) (c) nr	(a) 10 (b) 9 (c) 10	(a) uraemic, hyperprolactinaemia (b) uraemic, normoprolactinaemic (c) female hospital employees	RIA	(a) & (b) age, SEC, marriage, & (c) age	(a) & (b) (8 am) (c) nr	KSQ
Uvnäs -Moberg et al. (1990)	(a) 27(3.5) (c) nr	(a) 50 (c) 66	(a) 4-day post-partum (c) nr	RIA	(a) & (b) age.	(a) (10 am) (c) nr	KSP
Reavely et al. (1997)	(a) 38.6 (b) 53.7	(a) 65 (b)26	(a) hyperprolactinaemia (b) normoprolactinaemic pituitary disease	nr	n/a	(a) & (b) nr	SCL-90
Groër (2005)	(a) 28.9 (b) 23.4 (c) 23.8	(a) 84 (b) 99 (c) 33	(a) breast-feeding (b) bottle feeding (c) healthy, non-post-partum non-patient female student nurses	ELISA	n/a	(a) (8–11 am) (b) & (c) nr	POMS
Barry et al. (2014)	(a) 30.03(5.49) (b) 29.85 (5.88)	(a) & (b) 33	(a) & (b) moderately subfertile, mostly PCOS	ECLIA	(a) & (b) no meds, age, SEC, anx, stress, ethnicity	nr	AQ

RIA: radioimmunoassay.
ELISA: enzyme-linked immunosorbent assay.
ECLIA: electrochemiluminescence immunoassay.
SEC: socioeconomic class.
Time of blood sample: time of day in which blood was taken is identified.
AQ = Aggression Questionnaire (Hostility subscale).
KSQ = Kellner Symptom Questionnaire (Hostility subscale).
KSP = Karolinska Scales of Personality (Aggression–Hostility subscale).
POMS = Profile of Mood States (Anger subscale).
SCL-90 = Symptoms Checklist (Hostility subscale).
nr = not reported.
[a]This study also matched age, but in decades.

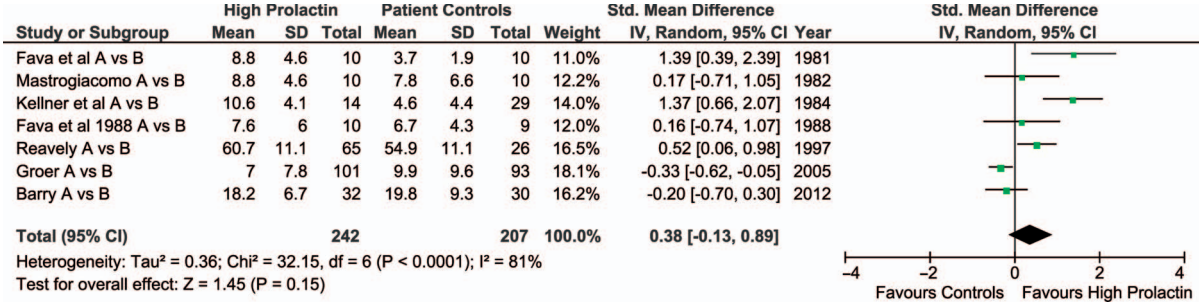

Figure 1. Forest plot of women's hostility levels in the seven studies of patients with high levels of PRL compared with patients with normal levels of PRL.

could be analysed using a fixed-effects model. The effect size was measured as the standard mean difference, calculated using Hedges' *g*. Like Cohen's *d*, a Hedges' *g* of 0.2 can be considered a small difference; 0.5, a moderate difference; and 0.8 or more, a large difference between groups. Note that these effect size values indicate statistical effect size rather than clinical effect size.

Results

Studies of PRL and aggression, hostility or anger ($n = 1065$) were retrieved. Of these, 632 were duplicates, and of the remaining 433, a further 426 studies did not meet the inclusion criteria, leaving a total of 7 studies. One article (Barry et al. 2014) was unpublished at the time but met the inclusion criteria, so was included. Eight studies with a total of 576 participants (242 women with high PRL, 207 patient controls and 127 healthy controls) qualified for review according to the inclusion criteria. The patient control groups (as opposed to healthy control groups) in these studies consisted of women with a variety of conditions (e.g., galactorrhoea, menstrual dysfunction, infertility, pituitary abnormalities, micro-adenoma, uraemic women on dialysis and caesarean section) as well as women in the immediate post-partum period being visited in their homes by researchers, and women attending a family practice. Not all of them were hospitalised patients or had an illness (e.g., the post-partum group), but all were under some type of medical supervision so the term 'patient' was applied to all, albeit somewhat loosely.

Regarding raw data from studies, Moss et al. (1990) did not report means and SDs in a table, but Figure 1 of their article clearly depicts this information. Regarding duplication of previous published findings: although findings from the patient control group of Mastrogiacomo et al. (1982) were original and unpublished, two of the groups (high PRL and healthy controls) duplicated data published by Fava et al. (1981). Thus a comparison of the latter two groups was excluded from the present meta-analysis in order to avoid duplication of analyses.

Table I shows the characteristics of the included studies.

Table II shows the methodological quality of the included studies, based on adapted NOS criteria. There was generally good agreement between the raters regarding NOS scoring, and any scoring not agreed upon was discussed and resolved.

Main outcomes

Figures 1, 2 and 3 show forest plots and test statistics for the comparisons. Based on heterogeneity scores, outcome variables were meta-analysed using random-effects models. Table III summarises the results of the meta-analyses.

Table III shows that there were non-significantly higher hostility levels in the women with high PRL compared with those in patient controls ($Z = 1.45$, $p < 0.15$; Hedges' $g = 0.38$; 95% CI: −0.13–0.89). There was significantly higher hostility in the high PRL group compared with that in healthy control women ($Z = 1.94$, $p < 0.05$; Hedges' $g = 0.72$; 95% CI: −0.01–1.45), and significantly higher hostility in patient controls compared with that in healthy controls ($Z = 1.94$, $p < 0.05$; Hedges' $g = 0.47$; 95% CI: 0.00–0.94). There was considerable heterogeneity in the findings of these studies, with I^2 values ranging from 57% to 86%. The

Table II. Evaluation of the methodological quality of the eight studies comparing high PRL and patient controls included in the meta-analysis using the NOS. The study that did not have patient controls, Uvnäs -Moeberg et al. (1990), is also assessed.

Study	Case definition adequate	Representativeness of cases	Selection of controls	Definition of controls	Comparability of both groups	Ascertainment of PRL levels	Same ascertainment method for all groups	Non-response rate	NOS Score
Fava et al. (1981)	X	X	*	*	*(no meds)	*	*	X	6
Mastrogiacomo et al. (1982)	*	*	*	*	X	*	*	X	6
Kellner et al. (1984)	*	X	*	X	X	*	X	X	3
Fava et al. (1988)	*	X	*	*	**(anx, no meds)	*	*	X	7
Uvnäs -Moeberg et al. (1990)	*	X	X	X	*(anx)	X	X	X	2
Reavely et al. (1997)	*	X	*	*	X	X	*	*	5
Groër (2005)	X	X	*	X	X	*	*	X	3
Barry et al. (2014)	*	X	*	*	**(anx, stress)	*	*	X	7

Case definition adequate: description of PRL levels in high PRL group and how levels were measured from at least one source (medical records, etc.).
Representativeness of cases: either random sample from complete sampling frame, or consecutive cases.
Selection of controls: for the purposes of this meta-analysis, a star is given for a patient control rather than community control.
Definition of controls: PRL levels measured in controls to assess their levels.
Comparability of both groups: give a star for any of the following: anxiety, life stress, psychiatric medication and pain.
Ascertainment of PRL levels: method of assay described for high PRL and patient controls.
Same ascertainment method for all groups: method of assay is similar in high PRL and patient controls.

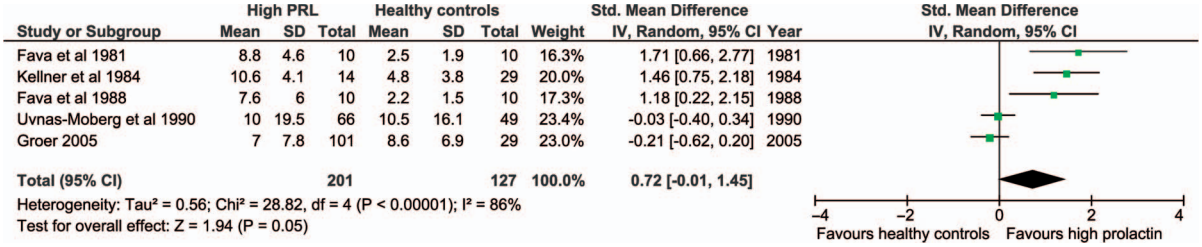

Figure 2. Forest plot of women's hostility levels in the five studies of patients with high PRL compared with healthy controls.

Table III. Results of the meta-analyses for the comparison among the three groups (high PRL group, patient controls and healthy controls).

Analysis	Number of studies	Hedges' *g* (95% CI)	Z *(P)*	Chi² *(P)*	I²
Hostility in high PRL compared with *patient* controls	7	0.38 (−0.13–0.89)	1.45 ($P = 0.15$)	32.15 ($P < 0.0001$)	81%
Hostility in high PRL compared with *healthy* controls	5	0.72 (−0.01–1.45)	1.94 ($P = 0.05$)	28.82 ($P < 0.00001$)	86%
Hostility in *patient* controls compared with *healthy* controls	5	0.47 (0.00–0.94)	1.94 ($P = 0.05$)	9.28 ($P < 0.05$)	57%

Notes: random-effects model used for all three comparisons due to high heterogeneity.

confidence intervals crossed zero in two of the three subgroup analyses.

Tables IV and V show the mean (SD) PRL and hostility scores in the groups.

Figure 4a shows the funnel plot for the studies comparing hostility in women with high PRL compared with patient controls, and Figure 4b shows the funnel plot for the studies comparing hostility in women with high PRL compared with that in healthy controls. Both Figure 4a and b show asymmetric funnel plots, with the smaller studies from the 1980s (cluster of studies at lower right of graphs) showing the largest effect sizes, whereas the larger studies from the 1990s onwards (clustered in upper middle/left) show more conservative findings (smaller Hedges' *g*). However, the clustering is weaker in 4(a), and perhaps not much regarding publication bias can be concluded from these funnel plots given the considerable heterogeneity in the findings (Terrin et al. 2003). The funnel plot for the comparison between patient controls and healthy controls is almost identical to that in Figure 4b. It can be interpreted in the same way as Figure 4b, and is not shown here in order to conserve space.

Discussion

This meta-analysis assessed studies that compared levels of hostility in women with different levels of PRL. It was found that women with high PRL levels report more hostility than women with normal PRL levels. However, the apparent effect of PRL on hostility was reduced almost by half when patient controls were used as the comparator instead of healthy controls. In statistical terms, the Hedges' *g* was reduced from a moderate-to-large effect size (Hedges' $g = 0.72$) to a moderate-to-small effect size (Hedges' $g = 0.38$) when controlling for patient status. Thus, roughly half of the hostility seen in the high PRL groups can be accounted for by the fact that participants are women with health issues rather than women who are healthy. The remaining effect size not explained by patient status (a Hedges' *g* of 0.34) may be attributable to PRL, or perhaps to a combination of PRL and other unknown factors. However, the fact that the confidence intervals crossed zero in both of these subgroup analyses and the substantial heterogeneity in the findings indicates that confidence in the validity of these findings should be tempered with caution. On the other hand, the finding of significantly higher hostility in the patient control group

Table IV. Mean and SD hostility levels in the three groups.

		High PRL group			Patient controls			Healthy controls		
Study	Scale	Mean	SD	N	Mean	SD	N	Mean	SD	N
Fava et al. (1981)	KSQ	8.8 [b]	4.6	10	3.7 [b]	1.9	10	2.5 [b]	1.9	10
Mastrogiacomo et al. (1982)[d]	KSQ	8.8 [b]	4.6	10	7.8 [b]	6.6	10	2.5 [b]	1.9	10
Kellner et al. (1984)	KSQ	10.6 [b]	4.1	14	4.6[b]	4.4	29	4.8 [b]	3.8	29
Fava et al. (1988)	KSQ	7.6 [b]	6.0	10	6.7[b]	4.3	9	2.2 [b]	1.5	10
Uvnäs -Moberg et al. (1990)	KSP	10.0 [e]	19.5	66	–	–	–	10.5 [e]	16.1	49
Reavely et al. (1997)	SCL-90	60.7[b]	11.1	65	54.9[b]	11.1	26	–	–	–
Groër (2005)	POMS	7.0	7.8	101	9.9	9.6	93	8.6	6.9	29
Barry et al. (2014)	AQ	18.2 [b]	6.7	32	19.8 [b]	9.3	30	–	–	–

AQ = Aggression Questionnaire. Scores.
KSQ = Kellner Symptom Questionnaire. Based on the above four studies, the mean (SD) norm = 3.1 (2.5), and upper limit of normal (mean + 2SD) = 8.1.
KSP = Karolinska Scales of Personality.
POMS = Profile of Mood States.
SCL-90 = Symptoms Checklist.
[a]Below normal range.
[b]Within normal range.
[c]Above normal range.
[d]Comparison between high PRL group and controls omitted from analysis because it duplicates that of Fava et al. (1981).
[e]No normative data available for KSP.

Table V. Mean and SD observed in PRL levels in the groups based on high versus low PRL levels. Units of PRL are in mIU/L.

	High PRL			Patient controls			Healthy controls		
Study	Mean	SD	N	Mean	SD	N	Mean	SD	N
Fava et al. (1981)[d]	>636[c]		10	<318[b]		10	Not given		10
Mastrogiacomo et al. (1982)	>636[c]		10	Not given		10	Not given		10
Kellner et al. (1984)	3180[c]	267	14	Not given			272.19[b]	129.21	26
Fava et al. (1988)	>1060[c]		10	527.5[c/b]		9	Not given		10
Uvnäs -Moberg et al. (1990)	Not given		49	–	–	–	Not given		66
Reavely et al. (1997)	>500[c]			Not given			–	–	–
Groër (2005)	Not given		–	–	–		Not given		
Barry et al. (2014)	430.52[b]	309.16	33	181.54[b]	40.54	33	–	–	–

Note: conversions for PRL: ng/mL*21.2 = mIU/L. (mIU/ml = mU/L = IU/L).
[a]Below normal range.
[b]Within normal range (102–496 mIU/L).
[c]Above normal range.
[d]Group C data not presented.

compared with that in the non-patient control group (a Hedges' *g* of 0.47) supports the suggestion that patient status explains at least a small-to-moderate (a Hedges' *g* of between 0.34 and 0.47) amount of the hostility seen in this meta-analysis. Although there was a substantial amount of heterogeneity ($I^2 = 57\%$), the confidence intervals did not cross zero, thus lending some statistical validity to the finding of this subgroup analysis.

Sometimes heterogeneity can be accounted for by differences in the methodology employed in the studies, and the heterogeneity seen in the findings of the present study may be an example of this. In general, the methodological quality of the included studies was acceptable (a median NOS score of five out of nine). One study (Uvnäs-Mobcrg et al. 1990) scored only two NOS stars, mainly because there were no patient controls and the healthy controls from a population norm. More importantly, an inspection of the characteristics of the eight studies highlights several ways in which they differed from one another. These differences were seen in five areas: (1) studies varied in the range of PRL levels included in their comparisons; (2) half of the studies used the same measure of hostility (the Kellner Symptom Questionnaire [KSQ]), but the others used various other measures of hostility; (3) half of the studies used exactly the same assay method, but the other studies used slightly different assays; (4) half of the studies had small sample sizes ($N < 50$); and (5) the characteristics of the women in the high PRL groups varied across studies. Closer inspection, in the following paragraphs, of the details of these differences will allow some sense of the degree to which these differences may influence how the findings can be interpreted.

Studies varied in the range of PRL levels used in their comparisons, and varied in how these levels were identified. It is possible that the effect of PRL on hostility is only seen when the levels are above the norm, yet not all studies included women with PRL

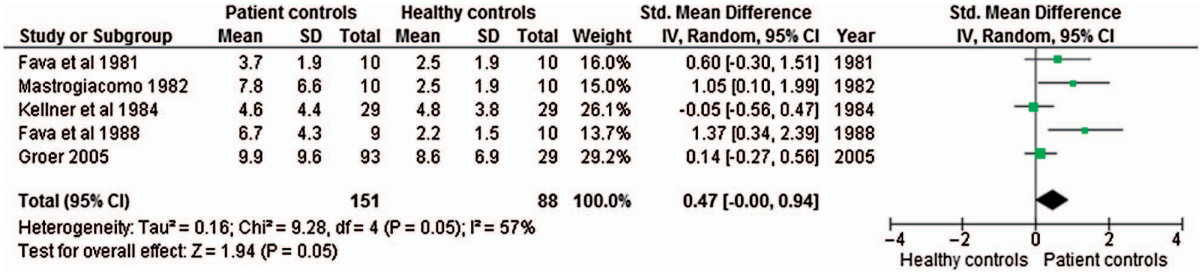

Figure 3. Forest plot of women's hostility levels in the five studies of patient controls compared with healthy controls.

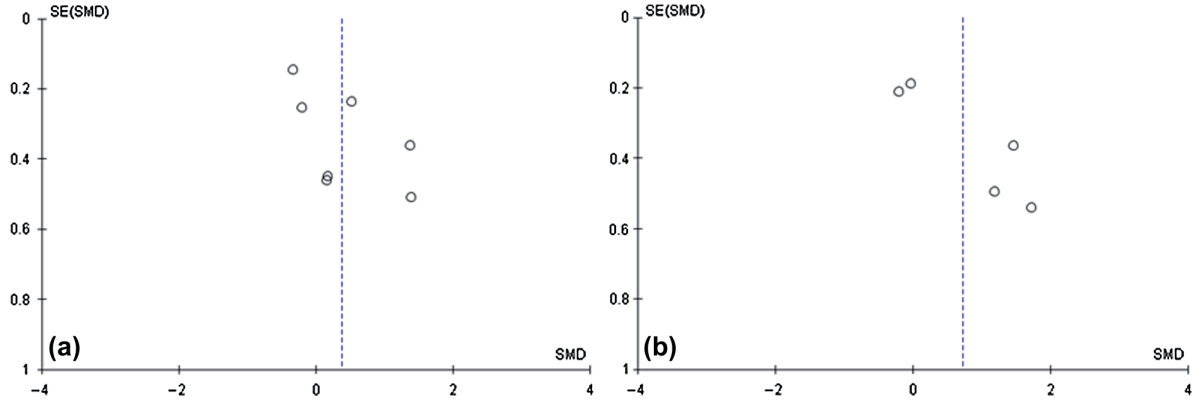

Figure 4. Figure a shows the funnel plot for the studies comparing hostility in women with high PRL compared with patient controls, and Figure b shows the funnel plot for the studies comparing hostility in women with high PRL compared with that in healthy controls.

levels verifiably above the norm. This could explain why some studies, which did not assess abnormally high PRL, did not find a relationship between PRL and hostility. Furthermore, most studies included at least one group in which PRL levels are inferred rather than measured. For example, Table V shows that, for the high PRL group, two studies did not provide any information on the PRL levels (Uvnäs-Mobcrg et al. 1990; Groër 2005). PRL levels were not measured in three of the six patient control groups, and were not measured in five of the six studies that used healthy controls, but were simply presumed to be normal. Also, in one study only a minority of the high PRL group had levels above the normal range (Barry et al. 2014). The uncertainty introduced by this disparity in definition of the groups may have contributed to the heterogeneity in the findings, though contrary to this suggestion, the removal of the Barry et al.' data in fact slightly increases the I^2 value. Apart from the issue of heterogeneity in the present meta-analysis, accurately measuring and verifying all of the participants' PRL levels increases the clinical and scientific value of a study. Nevertheless, despite the lack of uniformity across these studies, they still offer valuable insights. The studies of high PRL due to medical conditions (Kellner et al. 1984; Fava et al. 1981; Fava et al. 1988) are of importance to our understanding of the psychopathology of PRL, and the studies of PRL values within the normal range (Barry et al. 2014) or in post-partum women (Groër 2005; Uvnäs-Mobcrg et al. 1990; Mastrogiacomo et al. 1982) are of importance to our understanding of the normal psychobiology of PRL. Future studies need to measure PRL values in all participants and allocate them to their corresponding groups. Furthermore, future research relating PRL to hostility in women while hospital patients compared to when they are healthy again would be of value as this would further elucidate the impact of patient status on the relationship between these variables.

Different types of hostility questionnaire were used; four of the studies were consistent in the way they measured hostility, all using the KSQ (Kellner et al. 1984; Mastrogiacomo et al. 1982; Fava et al. 1981; Fava et al. 1988). Although the items in the KSQ are not dissimilar to items from other hostility questionnaires, it may be that this measure is particularly sensitive to the relationship between PRL and hostility. Table V shows that the scores were within the known norms for all groups, whichever questionnaire was used (apart from the questionnaire used in one study for which a norm is not known (Groër 2005)). Future studies of PRL and hostility should consider using the KSQ because it has proved to yield consistent findings in this field.

Ideally, every study would use the same type of assay for PRL. Some consistency was evident in the included studies, in that three of the studies (Kellner et al. 1984; Mastrogiacomo et al. 1982; Fava et al. 1981; Fava et al. 1988) used the same assay method (a radioimmunoassay [RIA] kit from Biodata, Italy). (One of the four studies from this group of authors, [Kellner et al. 1984] did not state the assay used). The other studies used assays from other manufacturers, but it is unlikely that differences in the assay manufacturer or method will have contributed to the heterogeneity seen in the meta-analysis. Nevertheless, future studies are best advised to use the gold standard assay method.

Four studies that found the largest effect had small samples, that is, sample sizes below 50 (Fava et al. 1981; Fava et al. 1988; Mastrogiacomo et al. 1982; Kellner et al. 1984), and the four studies that found weak or no effects had sample sizes over 50 (Reavley et al. 1997; Groër 2005; Uvnäs-Mobcrg et al. 1990). This might suggest that the apparent effect of PRL on hostility may in part be due to 'small studies effects', and this would imply ungeneralisable findings due to selection bias. However, the small studies were relatively heterogeneous within their methodology and findings; we might conclude that it would be valid to generalise their findings to populations of women similar to those participating in those studies. Nonetheless, future studies should be guided by a formal sample size calculation and, as a general rule, recruit sample sizes of fifty at a minimum. Also, a future meta-analysis on this topic will be improved by an increased overall sample size.

Characteristics of the women in the high PRL groups varied across studies. It is noteworthy that the meta-analysis found that the difference in hostility levels in the three groups (high PRL, patient controls and healthy controls) is explained to some degree by whether the participants were under some kind of medical care or whether they were healthy. Table I shows that the characteristics of the participants in the high PRL groups in the different studies vary by more than just PRL; most women in the high PRL groups had medical conditions, whereas two of the high PRL groups were of healthy post-partum women (Groër 2005; Uvnäs-Mobcrg et al. 1990). Indeed, a potential confounder of this study is that the control groups contained patients with conditions that might reflect abnormalities in the pituitary–gonadal axis. Table I shows that, for example, control groups contained women with polycystic ovary syndrome, normoprolactinaemic pituitary disease and subfertility. Although each of these control groups can be justified to some extent, the heterogeneity of conditions is not ideal in comparative studies. It is notable that the effect of PRL on hostility was generally seen most clearly in former rather than the latter type of group. In fact, the removal of the two studies of post-partum women from the comparison of high PRL to healthy controls improves the I^2 value from 86% to 0%, which narrows down the source of heterogeneity considerably, at least for the comparison of high PRL patients to healthy controls. On the other hand, removing the post-partum studies from the comparison of high PRL with patient controls and patient controls with healthy controls changes the I^2 value, but only modestly, from 81% to 76% and increases from 57% to 69%, respectively. The role of patient status in the relationship between PRL and hostility is particularly interesting, given the relationship between stress and PRL: stress induces PRL release (in animal models) and subsequently diminishes the stress response (Donner et al. 2007; Torner et al. 2004). It is, therefore, essential that future research adequately control for the impact of stress, particularly the stress related to patient status.

Future studies might also consider measuring neuroticism in addition to hostility, as scores on the two measures may be correlated (Felsten 1996). A relationship between hostility and PRL may also be found between neuroticism and PRL, suggesting that susceptibility to stress may be the underlying cause of a relationship among PRL, hostility and neuroticism.

Any one of five factors described above may have increased the heterogeneity, but their combination probably makes heterogeneity difficult to avoid. However, it appears that one source of heterogeneity comes from the inclusion of the post-partum studies, at least for the comparison of high PRL to healthy controls, indicating that these studies may best be considered separately from studies of patients with medical conditions. In any case, some degree of heterogeneity is often seen in meta-analyses, and does not usually invalidate findings regarding the main outcomes of interest. Thus, the findings regarding the impact of PRL and patient status on hostility should be accepted, but with appropriate caveats regarding the type of patient population being assessed.

A potential limitation of this meta-analysis is that some of the included studies did not control for age or disease type. However, levels of PRL are relatively stable in women during their reproductive years, and because none of the studies that reported age compared premenopausal women with post-menopausal women, it remains uncertain whether age was a confounding variable in those studies. Also, not all of the studies controlled for disease

type, that is, some studies did not compare identical disease types in high and low PRL groups, meaning that we cannot be sure if the findings in these studies were related to differences in disease type rather than PRL. In general, the studies would have been improved by using an anxiety measure as a covariate to measure changes in PRL related to the stress of having a disease.

It is interesting to consider how the findings might relate to the everyday clinical care of patients. The findings from the comparison of patients with normal PRL to healthy controls might lead one to the conclusion that people who are under medical care may be more hostile than healthy people. It is known that pain, stress and medication may increase PRL levels (Torre and Falorni 2007; Biondi and Picardi 1999; Del Pozo and Brownell 1979). It is also known that the type of pain experienced by a patient influences how much these negative feelings are felt and expressed (Pilowsky and Spence 1976). Research by Folkman & Lazarus (Folkman and Lazarus 1980) suggests that hostility and aggression are characteristics of a confrontive coping style. Confrontive coping is described by Guthrie and Nayak (Guthrie and Nayak 2012) as one of the coping styles used by people in reaction to their physical illness. Hospitalised patients using this method of coping might present as being aggressive in help-seeking behaviour and hostile in relation to health professionals. Perhaps, it might be useful for such a patient to learn more acceptable coping strategies or relaxation training. From the point of view of everyday patient care, it may be preferable to treat hostility at a psychological level rather than a hormonal level.

Although one in four people with physical illness go on to develop a mental illness due to the stress of the physical illness (Guthrie and Nayak 2012), there is relatively little research into how the stress of having a medical condition, or being in medical care, contributes to a patient's feelings of hostility. Future studies might explore this important issue further because it has a bearing on patient care, the doctor–patient relationship and the working environment of all those in contact with distressed patients. We might infer that because in many cases the source of a patient's hostility is related to their physical discomfort rather than dissatisfaction with their care, it is probably important for health professionals to not blame patients for hostility or to not take hostility from patients personally.

In conclusion, this meta-analysis suggests that PRL may be associated with a female patient's level of hostility. It also appears that the various stressors that are part of being under medical care may increase PRL and hostility in patients. Further high-quality, well-controlled research is required in order to identify definitively the precise magnitude of the effect of PRL on hostility.

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