Frontiers in Neuroendocrinology 54 (2019) 100775

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Demographic, sampling- and assay-related confounders of endogenous oxytocin concentrations: A systematic review and meta-analysis

Sinha Engel[a,*], Sebastian Laufer[a], Robert Miller[b], Helen Niemeyer[a], Christine Knaevelsrud[a], Sarah Schumacher[a]

[a] Division of Clinical Psychological Intervention, Department of Education and Psychology, Freie Universität Berlin, Schwendenerstr. 27, 14195 Berlin, Germany
[b] Chair of Biopsychology, Faculty of Psychology, Technische Universität Dresden, Zellescher Weg 19, 01069 Dresden, Germany

ARTICLE INFO

Keywords:
Covariate
Extraction
Specimen
Sex
Age
Sampling
Nicotine, Smoking
Diurnal rhythm
Time of day

ABSTRACT

Studies on endogenous oxytocin concentrations are often criticized for the debatable comparability between specimens and the variation in reported values. We performed meta-regressions on $k = 229$ studies ($n = 12\,741$ participants), testing whether specimen, extraction, sex, age, time of day, or fasting instructions influenced oxytocin measurements. Predicted oxytocin concentrations differed depending on specimen and extraction: Measurements were extremely high in unextracted blood, compared to extracted blood and other specimens. Measurements were higher in samples with more female participants and higher age. Instructions not to smoke before sampling were correlated with higher oxytocin in unextracted samples. There was no impact of instructions to refrain from eating, drinking, consume caffeine, alcohol or exercising. Oxytocin concentrations increased from morning to afternoon. Our results showed that oxytocin is differentially reflected in blood, saliva, urine and cerebrospinal fluid. Extraction impacts oxytocin measurements, particularly in blood. Considering relevant confounders might increase comparability between studies.

1. Introduction

The neuropeptide oxytocin is an important agent in clinical psychoneuroendocrinological research. There is a large body of research investigating endogenous oxytocin concentrations as a possible indicator of neuroendocrine dysregulations in patients with mental disorders (Cochran et al., 2013). At the same time, the reliability of this approach has been strongly disputed (McCullough et al., 2013).

Oxytocin is synthesized in magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus. From there, it is transmitted to the posterior lobe of the pituitary and released into the bloodstream (Brownstein et al., 1980). Peripheral oxytocin receptors have been identified in the reproductive organs, mammary tissue, kidney, heart, thymus, fat cells, pancreas and adrenal gland (Gimpl and Fahrenholz, 2001; Jurek and Neumann, 2018; Song and Albers, 2018). In addition to its function as a hormone, oxytocin acts centrally as a neurotransmitter and neuromodulator. From both, magnocellular neurons of the hypothalamic paraventricular and supraoptic nuclei and parvocellular neurons of the paraventricular nucleus, it is directly transmitted to various brain sites (Knobloch and Grinevich, 2014).

A variety of complementary methodological approaches is available to determine oxytocin's functions. In animal models, brain site-specific effects of endogenous oxytocin can be determined by means of microdialysis, as well as oxytocin receptor agonist or antagonist injections (Lee et al., 2008; Neumann, 2008). In addition, behavioral consequences of synthetic oxytocin injection to different brain regions can be observed (Neumann, 2008). The methodological approaches available in human research measure oxytocin's effects in a less specific manner. Intranasally administered synthetic oxytocin passes the blood-brain barrier (Born et al., 2002), but targets a variety of brain sites through different pathways (Quintana et al., 2015). Therefore, behavioral consequences can only be interpreted brain site-unspecifically. Endogenous oxytocin concentrations can be measured in different body fluids, such as blood, saliva, urine, and cerebrospinal fluid (McCullough et al., 2013), but, again, these effects cannot be attributed to specific central mechanisms of action.

1.1. Oxytocin's behavioral and psychological functions

Besides oxytocin's role in physiological processes such as birth and

* Corresponding authors at: Technische Universität Dresden, Zellescher Weg 19, 01069 Dresden, Germany (R. Miller).
E-mail addresses: s.engel@fu-berlin.de (S. Engel), sebastian.laufer@fu-berlin.de (S. Laufer), robert.miller@tu-dresden.de (R. Miller), hniemeyer@zedat.fu-berlin.de (H. Niemeyer), christine.knaevelsrud@fu-berlin.de (C. Knaevelsrud), sarah.schumacher@fu-berlin.de (S. Schumacher).

https://doi.org/10.1016/j.yfrne.2019.100775
Received 26 November 2018; Received in revised form 22 July 2019; Accepted 23 July 2019
Available online 25 July 2019
0091-3022/

lactation (Kendrick et al., 1988), it influences key behavioral and psychological processes related to mental well-being.

1.1.1. Evidence from animal studies

Fear conditioning and safety learning paradigms have been used to study oxytocin's anxiolytic effects and related them to oxytocin receptor expressing structures of the neural fear network (Eckstein et al., 2019; Maroun and Wagner, 2016). For instance, central administration of synthetic oxytocin to rats prior to fear acquisition enhanced, whereas injection of an oxytocin receptor antagonist impaired extinction. Oxytocin administration after fear acquisition, on the other hand, impaired extinction, indicating a time-dependency of the effects (Toth et al., 2012). Additionally, a region-dependency was detected when studying the effects of synthetic oxytocin and oxytocin receptor agonist injection to rats' infralimbic prefrontal cortex, basolateral and central amygdala pre- and post-fear acquisition on extinction (Lahoud and Maroun, 2013). In summary, these results show that, depending on temporal dynamics, oxytocin has anxiolytic effects that are mediated via its receptors at different brain sites.

In addition, oxytocin modulates the endocrine stress response (Engelmann et al., 2004; Hostinar et al., 2014; Winter and Jurek, 2019). Increased oxytocin release in the paraventricular nucleus of the hypothalamus in response to stress was observed in male rats (Babygirija et al., 2012). This process is assumed to downregulate neuroendocrine stress responses, as in virgin rats, intracerebroventricular infusion of an oxytocin antagonist increased secretion of corticotropin and corticosterone both under basal conditions and in response to stress (Neumann et al., 2000). Moreover, originating from research that linked centrally injected synthetic oxytocin to maternal behavior of rats (Pedersen et al., 1992) or to partner preferences of female monogamous prairie voles (Williams et al., 1994), oxytocin became known for its prosocial effects (Baribeau and Anagnostou, 2015; Heinrichs et al., 2009; Macdonald and Macdonald, 2010).

1.1.2. Transfer to human studies

Oxytocin's anxiolytic, stress-reducing and prosocial effects were also transferred to human subjects:

Intranasal oxytocin administration after fear acquisition enhanced extinction recall (Acheson et al., 2013) and increased prefrontal cortex and electrodermal activity during the early extinction phase, followed by a stronger decline of electrodermal activity (Eckstein et al., 2015).

Oxytocin's modulation of the human endocrine stress response seems to be particularly relevant in social contexts: Intranasal oxytocin administration led to lower cortisol concentrations, along with decreased subjective stress, in response to a social stress paradigm in healthy men (Heinrichs et al., 2003). In addition, it decreased the cortisol response of heterosexual partners during a couple conflict paradigm and promoted positive communication (Ditzen et al., 2009). Concerning its prosocial effects, oxytocin has been associated with more complex social behaviors in humans. Examples include a promotion of trust, as investigated by means of intranasal administration in relation to trust game paradigms (Baumgartner et al., 2008; Kosfeld et al., 2005), or an involvement in romantic attachment as investigated by means of elevated endogenous oxytocin concentrations measured in newly attached romantic partners compared with singles (Schneiderman et al., 2012). However, it is worth noting that oxytocin's functions vary between persons and contexts rather than being beneficial for social behavior in general (Olff et al., 2013).

1.2. How reliable is current research on endogenous oxytocin?

Impairments in fear processing, stress coping and social behavior are characteristics of several mental disorders. Therefore, oxytocin appears to be an interesting target for clinical researchers. The most frequently applied approach to investigate the endogenous oxytocin system in humans is to measure endogenous oxytocin concentrations in blood, saliva, urine, or CSF. To date, a number of studies have used this approach to investigate dysregulations of the oxytocin system in clinical populations (Cochran et al., 2013). However, the reliability of measuring endogenous oxytocin concentrations has been strongly questioned (McCullough et al., 2013; Szeto et al., 2011).

For instance, it remains unclear whether peripheral measures reflect the central availability of oxytocin. This is of particular relevance for biomarker research, as oxytocin's psychological functions are assumed to be regulated by its central actions (Meyer-Lindenberg et al., 2011). A recent meta-analysis underlined this concern, as it found no correlation between oxytocin concentrations from central and peripheral specimens under basal conditions (Valstad et al., 2017). Thus, basal peripheral concentrations do not seem to reflect central ones. However, correlations were found under challenged conditions. Such paradigms might be used to estimate central oxytocin release by means of peripheral measurements (Crockford et al., 2014; Valstad et al., 2017). Evidence from animal studies further emphasizes that the consistency between peripheral and central measurements crucially depends on the specific brain site investigated. For instance, early studies applying push-pull perfusion and microdialysis in rats showed that the increased peripheral availability of oxytocin during birth (Higuchi et al., 1986) was independent of oxytocin release in the septum and hippocampus (Landgraf et al., 1991), whereas it was successfully associated with oxytocin release in the supraoptic and paraventricular hypothalamic nuclei (Neumann et al., 1993b). In line with this, central injection of an oxytocin antagonist led to decreased suckling-induced oxytocin release in both the supraoptic nucleus and blood (Neumann et al., 1993a). Furthermore, increased oxytocin concentrations were found both in blood and in the hypothalamic supraoptic and paraventricular nuclei of rats in response to stress (Torner et al., 2017; Wotjak et al., 1998).

In addition, it is problematic that there is an extremely high variability of reported oxytocin values between studies, even within similar populations and contexts (Szeto et al., 2011). These inconsistencies can partly be explained by different measurement methods. Not only the correlation between central and peripheral specimens (Valstad et al., 2017), but also that between different peripheral specimens has been called into question (Hoffman et al., 2012). Furthermore, the comparability between studies that differ with regard to analysis (e.g. enzyme immunoassay (EIA) or radioimmunoassay (RIA)) and sample preparation (e.g. extraction) methods is doubtable (Leng and Sabatier, 2016; Szeto et al., 2011). Sample extraction precedes the actual peptide measurement and prevents matrix components and molecules other than oxytocin from being detected by the assay (Szeto et al., 2011). Various methods to extract samples exist (Cool and DeBrosse, 2003; Szeto et al., 2011). Comparisons showed that concentrations derived from unextracted samples were (several) hundred-fold higher than from extracted ones and that both measurements were uncorrelated (Robinson et al., 2014; Szeto et al., 2011). There are indications that measurements in unextracted samples are more influenceable by sampling-related factors (Robinson et al., 2014) and it was suggested that, next to oxytocin, assays detect multiple other immunoreactive products from unextracted samples (Szeto et al., 2011).

In addition to these methodological issues, potentially confounding variables, such as sex, age, time of day or fasting might influence measurements of endogenous oxytocin concentrations and therefore explain variability between studies. To date, a number of empirical studies has investigated these potential confounders of endogenous oxytocin concentrations, but this primary work has not been summarized in a systematic overview, yet.

Oxytocin's physiological and psychological functions relating to reproductive and sexual behavior (Veening et al., 2015) and its interactions with sex hormones (Patisaul et al., 2003) suggest sex differences in endogenous oxytocin concentrations. A review on interindividual differences in the response to intranasal oxytocin administration indeed mentioned that there are some indications that plasma oxytocin levels differ between the sexes (Macdonald, 2013). The idea that endogenous

oxytocin concentrations might vary with age has been discussed due to the role of oxytocin in attachment (Huffmeijer et al., 2013). Throughout the lifespan, persons are committed to various kinds of relationships and experience changes in their social roles. Interactions between these events and the oxytocin system seem evident. However, to date, it remains unclear whether there are age-related differences in endogenous concentrations (Huffmeijer et al., 2013). Concerning the possible role of the time of day of sampling as a confounder, there is only a small amount of data from humans, which does not allow definitive conclusions. Nevertheless, these data, as well as data from animal studies, indicate diurnal fluctuations, as suggested in a review on oxytocin's therapeutic potential (Macdonald and Feifel, 2013). Evidence from animal studies also indicate that food (Burlet et al., 1992), nicotine (Russell and Chaudhury, 1972), or caffeine intake (Wu et al., 2017) as well as physical exercise (Bakos et al., 2007) might impact oxytocin measures. Oxytocin's regulatory impact on metabolism and food intake has been extensively studied (Ding et al., 2018). Concerning the reverse impact of dietary behaviors on endogenous oxytocin concentrations, a recent review systematically described 13 primary studies on this topic, but, lacking sufficient data, could not provide an effect size (Skinner et al., 2018).

In conclusion, different kinds of specimen and assay-related aspects, such as sample preparation and analysis method, cause variation in reported values of endogenous oxytocin concentrations. Additionally, confounders of endogenous oxytocin might constitute a source of variance. As yet, there is no systematic overview of such confounders, and accordingly, guidelines in this field are lacking. Therefore, researchers presumably apply heterogeneous sampling protocols and statistically control for different variables in their analyses. This might explain the significant variation in concentrations reported by studies, decreasing the trust in the reliability of current clinical research on oxytocin (McCullough et al., 2013; Szeto et al., 2011).

1.3. Objectives

This is the first systematic review and meta-analysis to address these issues related to measurements of endogenous oxytocin. We performed meta-regressions to test whether possible heterogeneity in basal endogenous oxytocin concentrations of healthy humans might be explained by specimen, considering the impact of extraction. Moreover, we determined the impact of participants' sex and age, time of day of sampling, and fasting instructions. All analyses were controlled for assay-related variance.

According to the recommended reporting system by the PRISMA group (Moher et al., 2009), our main systematic research question can be described as follows: As population, we included healthy, adult and non-pregnant humans. We included studies without special consideration of intervention or comparison group. In terms of outcome, we extracted basal measures of endogenous oxytocin concentrations. We included between-, within-, and single-group designs.

2. Methods

2.1. Review protocol, data, analysis and results accessibility

We published a protocol explaining the rationale and methods of this systematic review and meta-analysis on PROSPERO (Registration number: CRD42017072306) on the 17th July 2017. It is available online at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017072306

Moreover, we published our data, analysis methods and results on an Open Science Framework repository on the 14th November 2018. It is available online at:

https://osf.io/4jsah/.

2.2. Eligibility criteria

Studies were eligible if they included a sample or subsample of healthy, adult (mean age ≥ 18 years) and non-pregnant humans. Samples or subsamples consisting of animals, children (< 18 years), persons with mental or physical illness or injuries, and pregnant or postpartum women (≤1 year after birth) were excluded. Studies applying reactivity designs (e.g. stress paradigms or pharmacological challenges) or evaluating an intervention (e.g. psychotherapy or pharmacotherapy) were included if they reported pre-challenge or pre-intervention basal oxytocin concentrations. We did not define any restrictions with regard to comparison groups. A single sample or subsample of participants meeting our criteria was sufficient for our study aims. In terms of outcome, studies were required to measure basal endogenous oxytocin concentrations in blood, saliva, urine, or CSF. Despite the problems associated with unextracted measurements (Leng and Sabatier, 2016; Robinson et al., 2014; Szeto et al., 2011), we included studies measuring oxytocin in extracted and unextracted samples in order to meet the standard of a comprehensive systematic review. We included studies applying between-, within- and single-group designs but excluded case studies and reviews. Published and unpublished studies in the English and German language were considered. There were no restrictions concerning publication year.

2.3. Identification and selection of studies

2.3.1. Information sources and electronic search strategy

The literature search was conducted following the search strategies recommended by Lipsey and Wilson (2001). We searched the following electronic bibliographic databases and registers up to 28th March 2017: *PsycINFO, PubPsych, PsycARTICLES, PubMed, Web of Science, BIOSIS, ProQuest Dissertations and Theses Global* and *Clinicaltrials.gov*. We searched titles, abstracts and keywords for the terms ((oxytocin) AND (blood OR plasma OR serum OR CSF OR cerebrospinal fluid OR urine OR urinary OR saliva OR salivary)). We searched the grey literature by examining the abstracts of conference contributions, posters and commentaries, and contacted experts in the field. Moreover, we screened reference lists of reviews and articles selected for inclusion in this review.

2.3.2. Study selection

In a first step, titles and abstracts were screened, excluding duplicates and studies meeting our exclusion criteria (i.e., studies published in languages other than English or German, animal studies, studies with children, studies with exclusively pregnant or post-partum women, studies with exclusively mentally or physically ill participants, reviews, qualitative studies, studies investigating biochemical micro-processes, e.g. in-vitro studies, studies that did not assess endogenous oxytocin, studies that did not assess endogenous oxytocin under basal conditions, study registers without reported data, and studies without available abstracts). Regarding study registers, we contacted the corresponding author to ask whether data were accessible and, if possible, included them in the screening process. If abstracts or full texts were not available, we contacted the corresponding author and requested access to the paper.

In a second step, full-text articles were screened to decide whether studies were eligible for inclusion.

In a third step, we descriptively summarized all eligible studies and included those with all necessary data obtainable in the meta-analytic procedure.

Steps one and two were performed by one researcher (SE). Step three was conducted as follows: Studies considered as eligible were randomized based on a computerized tool and assigned to a team of two researchers (SE and AW or SL and HK). Researchers within one team independently extracted data and, based on this, decided whether all information necessary for the meta-analytic procedure was obtainable.

In the case of disagreements, a third independent person (SL or SE, respectively) was consulted for the final decision.

2.4. Data extraction and preparation

2.4.1. Data collection process

Data from individual studies were extracted according to a predefined coding manual which the researchers had been trained to use. Extraction was performed by the same teams and using the same strategies as decisions regarding inclusion. If data were not accessible or values could only be estimated, the corresponding authors of the primary studies were contacted in order to gather as many data as possible and to obtain data that were as precise as possible. The authors were contacted by e-mail and a reminder was sent after 10 days if no reply was received. If authors were unable to provide us with the data or did not respond to the emails, we estimated the data if possible, or otherwise considered them as unavailable. Studies without available data or studies containing data that overlapped with other samples were descriptively summarized but excluded from the meta-analysis. With regard to overlaps, we first extracted data from all studies, and then included those studies which provided a larger sample or more useable data in the meta-analytic procedure.

2.4.2. Data items

In terms of our outcome measure, we extracted *M* and *SEM* of basal endogenous oxytocin concentrations. If studies reported more than one basal value, we extracted the chronologically first one. From crossover designs in which participants underwent different challenges in varying orders, we extracted values measured before their first challenge whenever possible. Otherwise, we picked one of the challenges at random and extracted the corresponding value that was gathered beforehand. If values were not reported in texts or tables but were shown in figures, we used an online plot digitizer (Rohatgi, 2015). This tool has been previously applied in a meta-analysis on endogenous oxytocin and yielded good results (Valstad et al., 2017). If *M* and *SEM* were not directly extractable, we estimated them from other descriptive parameters (i.e. *Md*, *SD*, *Var*, *Min,* and *Max*, (Hozo et al., 2005)) and transformed all units into pg/ml. For the respective formulas, see supplementary material 1.

We extracted sample sizes and considering assay-related variables, the type of specimen (blood, saliva, urine, or CSF), extraction (0 = no, 1 = yes), assay (e.g. EIA or RIA), location of the biochemical laboratory and assay manufacturer. If the assay manufacturer was not reported, the information was imputed from the laboratory location to enable the estimation of assay-related heterogeneity in oxytocin concentrations.

Regarding potential confounders, we extracted *M* and *SEM* of age and sex distribution of each sample. Furthermore, we extracted the time of sampling and whether participants were asked to refrain from eating, drinking, consuming caffeine, smoking, consuming alcohol, or exercising before sample collection. In addition, we extracted study type (e.g. journal article, dissertation), information about overlaps, and location of data collection.

2.5. Assessment of risk of bias and appropriateness to the aim of our study

Our inclusion criteria were defined with the aim of gathering a large and representative pool of studies. Therefore, we included studies with heterogeneous designs. As most validated tools for the assessment of risk of bias refer to specific study designs, there was no available tool which was appropriate to all studies in our pool. We did not wish to refrain from estimating study quality, as we consider this to be an important aspect of systematic reviews. Therefore, in line with the notion of the Weight of Evidence framework (Gough, 2007), we developed an instrument that included items on general study quality and the appropriateness to our study. To estimate general study quality, we used one item referring to the handling of missing data. To estimate the appropriateness to our study, we used two items referring to the assessment of physical and mental health, as health constituted a central inclusion criterion.

The rating process was carried out by the same teams and with the same strategies as decisions about inclusion and extraction. We used the final summary score of these three items, indicating quality and appropriateness to our review aims, as a regressor in our meta-regression in order to control for risk of bias and appropriateness to the study aim when estimating the influence of the respective confounders.

2.6. Meta-analytic procedure

We performed meta-regressions using our predefined potential confounders as sample-level regressors to explain between (sub-)samples heterogeneity in basal endogenous oxytocin concentrations in log-scaled pg/ml (Higgins et al., 2008).

In a first step, we defined a baseline regression model that served as the basis for all following analyses. It included two variance components to account for study-and assay-related heterogeneity. Study-related heterogeneity was considered as variance component as in some cases, we included several independent samples from the same study. Assay-related heterogeneity was considered as variance component to control for the impact of different laboratories, assay manufacturers and assay types (RIA or EIA). In this way, we ensured that the influence of the regressors added to the model was estimated irrespective of similarities within studies and differences between laboratories, assay manufacturers or assay types.

The baseline regression model included sample-level moderators representing specimen (reference: blood, comparisons: saliva, urine, CSF) and extraction (reference: unextracted samples). A highly accurate imputation model was fitted to handle missing values in the extraction variable. Main, as well as interactive effects of specimen and extraction were tested. In addition, the baseline regression model comprised main effects of the regressors year of publication (reference: 2 000 years AD, scale: 10 years), risk of bias and appropriateness score, and the standard error of the reported oxytocin concentration (in order to adjust for bias using the PET-PEESE method (Stanley and Doucouliagos, 2014)) as sample-level moderators.

In the following steps, we entered the possible confounders into the model as sample-level moderators. Sex was defined as a metric variable indicating the percentage of women per sample. The metric variable age was referenced at 30 years and scaled with 10 years. The metric variable time of day was referenced at 12 a.m./midnight and scaled with units of three hours. Instructions to fast were divided into seven variables: instructions to refrain from eating, drinking, consuming caffeine, smoking, consuming alcohol, or exercising, as well as one combined variable indicating whether any of these instructions was given. Fasting variables were coded dichotomously, indicating whether participants received the respective instructions (1) or not (0). Missing values in the fasting variables were imputed to 0, as we assumed that if no such instructions were reported in the paper, they were not given.

Unextracted blood was set as reference for all analyses of possible confounders. In order to test whether extraction moderated their possible impact, we performed subgroup analyses. This implies that the main analysis which was initially conducted across all primary studies was performed separately within those studies that used unextracted samples and within those that used extracted samples. All analyses were performed using the *metafor* package (Viechtbauer, 2017) and *R* statistical software (R Core Team, 2017).

3. Results

3.1. Study selection

The number of studies that were screened, assessed for eligibility, excluded for predefined reasons or included in the qualitative or

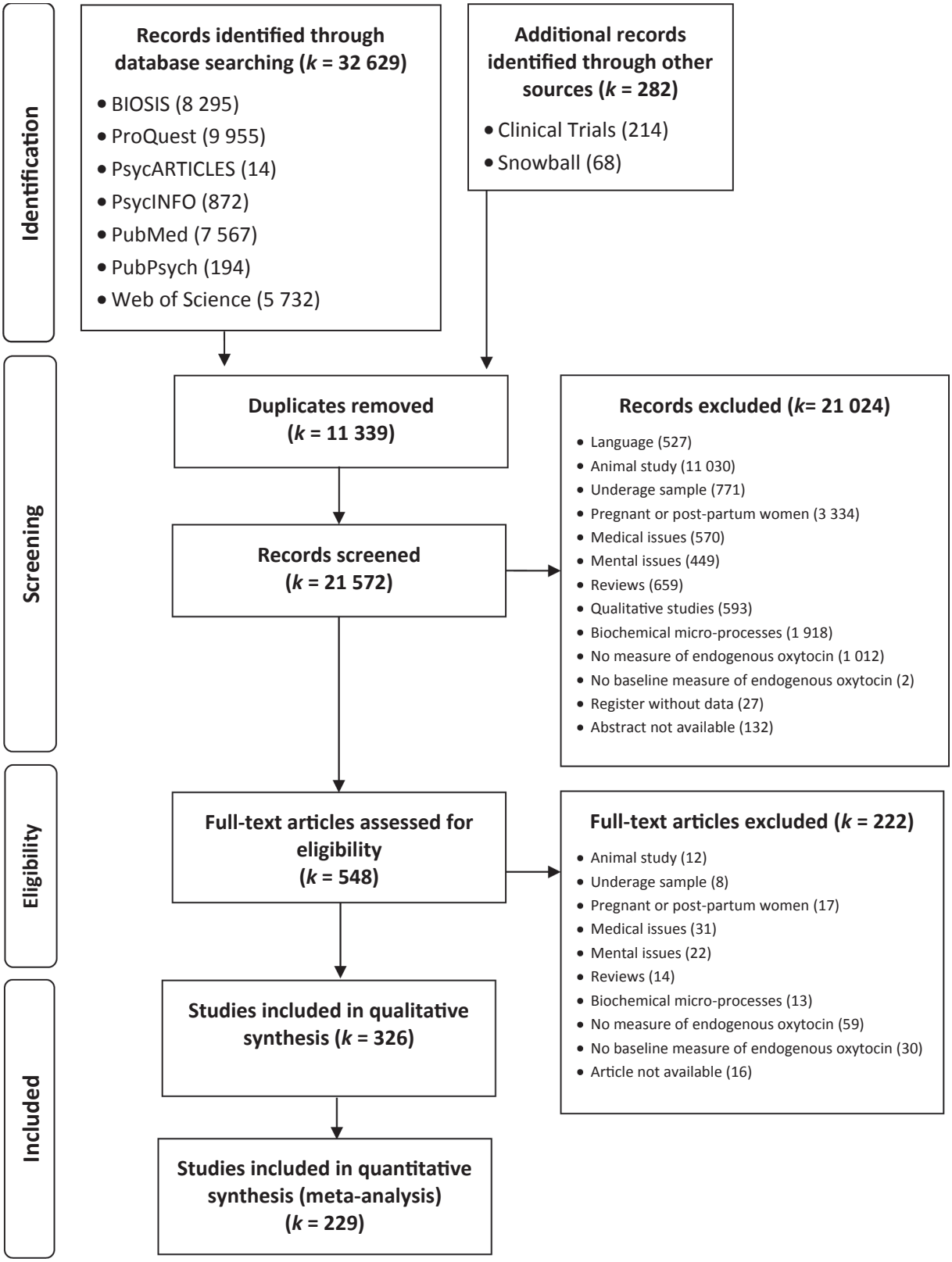

Fig. 1. Flow diagram of identification and selection of primary studies.

quantitative part of this review are shown in a flow diagram (Fig. 1). Supplementary material 2 contains the full reference list. We included 326 studies in the qualitative analysis and 229 studies (comprising 12 741 participants from 339 subsamples) in the meta-analytic procedure.

3.2. Description of primary studies and consideration of potential confounders

Table 1 shows the data of the 229 studies upon which the meta-analytic procedure was based. It reports size, age and sex distribution of

Table 1
Description of studies included in meta-analytic procedure.

Authors	Year	n[a]	% female[b]	Age M	Time of day[c]	Fast[d]	Fast[e]	Eat[e]	Drink[e]	Caffeine[e]	Smoking[e]	Alcohol[e]	Exercise[e]	Specimen	Oxy M[f]	OxySD[f]	Oxy Mlog[g]	Oxy SDlog[g]
Afinogenova	2015	34	100.00	23.90	N/A	Yes	1	0	0	0	0	0	0	Blood	1501.00	664.73	7.22	0.42
Ahmed et al.	2015	23	52.17	72.00	N/A	Yes	1	0	0	0	0	0	0	Blood	179.00	95.00	5.06	0.50
Altemus et al.	1999	26	46.15	35.00	9:00 am − 10:00 am	Yes	1	1	1	1	0	1	1	CSF	3.70	1.02	1.27	0.27
Altemus et al.	2001	8	100.00	34.20	7:50 am − 9:00 am	Yes	1	1	0	1	1	1	1	Blood	1.67	0.28	0.50	1.68
Althaus et al.	2016	30	0.00	22.60	9:10 am or 2:10 pm	Yes	0	0	0	1	1	1	0	Blood	0.68	0.78	−0.81	0.92
Amico, Seif & Robinson	1981a	17	0.00	N/A	Morning and afternoon	Yes	1	1	0	1	1	1	1	Blood	3.00	0.49	1.09	0.16
		8	100.00												2.85	0.34	1.04	0.12
		5	100.00												7.65	1.90	2.00	0.24
		5	40.00												35.32	5.70	3.55	0.16
Amico, Seif & Robinson	1981b	5	100.00	26.00	9:00 am	Yes	0	0	0	1	1	1	0	Blood	1.90	0.94	0.53	0.47
Amico et al.	1983	6	0.00	N/A	6:00 am	Yes	0	0	0	1	1	1	0	Blood	1.33	0.42	0.24	0.31
		6	100.00												2.50	1.22	0.81	0.46
Amico et al.	1985	18	100.00	N/A	N/A	N/A	0	0	0	0	0	0	0	Blood	1.33	0.63	0.18	0.45
		18	100.00												2.83	0.51	1.02	0.18
		18	0.00												1.22	0.42	0.14	0.34
		18	0.00												2.83	0.64	1.02	0.22
		5	100.00												1.33	0.16	0.28	0.12
		5	100.00												7.67	1.90	2.01	0.24
		4	100.00												0.50	0.20	−0.75	0.39
		4	100.00												2.67	0.54	0.96	0.20
		3	0.00												3.17	1.00	1.11	0.31
Amico & Johnston	1985	8	50.00	N/A	9:00 am − 10:00 am	Yes	1	0	1	1	1	1	0	Blood	2.17	0.48	0.75	0.22
		6	0.00												1.67	0.73	0.42	0.42
Amico, Ulbrecht, Robinson	1987	4	0.00	N/A	8:00 am	Yes	1	0	0	1	1	1	0	Urine	7.82	3.60	1.96	0.44
		9	N/A		9:00 am − 12:00 pm										17.00	6.99	2.76	0.40
		8												Blood	0.83	0.48	−0.33	0.54
Andari	2014	15	43.30	23.67	10:00 am	Yes	0	0	0	0	1	0	0	Blood	3.67	0.32	1.30	0.02
		20	N/A	N/A	N/A	N/A	0	0	0	0	0	0	0		1.50	0.18	0.41	0.03
Anderberg & Uvnäs-Moberg	2000	30	100.00	N/A	8:00 am − 9:00 am	Yes	1	0	0	0	0	0	0	Blood	18.14	4.70	2.87	0.25
Apter-Levi, Zagoory-Sharon & Feldman	2014	48	0.00	29.30	1:00 pm − 4:00 pm	Yes	1	1	0	0	0	0	0	Blood	391.18	159.72	5.89	0.39
Bagdy & Arato	1998	7	0.00	31.70	7:30 am	Yes	1	0	0	0	0	0	1	Blood	8.28	3.81	2.02	0.44
		5	100.00	33.00											6.49	1.77	1.83	0.27
Barraza	2010	144	51.00	20.80	1:00 pm − 4:00 pm	Yes	0	0	0	1	0	1	0	Blood	456.45	300.24	5.94	0.60
Beavin	2014	30	0.00	49.17	N/A	N/A	0	0	0	0	0	0	0	Blood	341.96	175.72	5.72	0.48
		56	0.00	21.66											1.97	2.15	0.29	0.89
Bello	2007	13	0.00	33.29	1:30 pm − 9:00 pm	Yes	1	1	1	1	0	1	0	Blood	281.60	95.55	5.58	0.33
Bello et al.	2008	14	0.00	N/A	1:30 pm − 9:00 pm	Yes	1	1	1	1	1	1	0	Blood	219.56	106.23	5.29	0.46
Bershad et al.	2015	11	54.55	22.50	9:00 am	Yes	0	0	0	1	1	1	0	Blood	37.80	45.77	3.18	0.95
		7	0.00	25.50											6.36	2.54	1.78	0.38
Bhandari et al.	2014	93	100.00	19.86	9:00 am or 12:00 pm or 3:00 pm	Yes	0	0	0	0	1	0	0	Saliva	2.65	1.32	0.86	0.47
Bialik	2007	30	53.30	28.70	N/A	N/A	0	0	0	0	0	0	0	Blood	129.70	71.70	4.73	0.52
Bick	2011	43	100.00	42.10	6:00 am − 8:00 pm	Yes	0	0	0	1	1	1	0	Urine	0.87	0.07	−0.14	0.08
Blagrove et al.	2012	17	50.00	20.45	10:00 pm	Yes	1	1	1	1	1	1	1	Saliva	12.63	3.35	2.50	0.26
Blaicher et al.	1999	12	100.00	N/A	N/A	N/A	0	0	0	0	0	0	0	Blood	11.53	6.08	2.32	0.50
Bosch et al.	2015	16	0.00	23.90	8:30 am	Yes	0	0	0	1	1	1	0	Blood	17.49	8.46	2.76	0.46
Bossmar, Forsling & Åkerlund	1995	10	100.00	55.20	7:00 am − 8:30 am	Yes	0	0	0	0	1	0	0	Blood	2.52	1.01	0.92	0.13
Breuil et al.	2014	1097	100.00	71.80	12:00 pm − 3:00 pm	No	0	0	0	0	0	0	0	Blood	1.00	1.90	−0.76	1.24
Breuil et al.	2015	552	0.00	65.00	8:00 am	Yes	1	1	1	1	0	1	0	Blood	7.81	9.40	1.61	0.95
Brondino, Fusar-Poli & Politi	2017	22	100.00	20.82	4:00 pm − 5:00 pm	Yes	1	1	1	1	1	1	1	Saliva	6.52	2.86	1.79	0.42
Cao et al.	2014	106	0.00	N/A	N/A	N/A	0	0	0	0	0	0	0	Blood	101.59	55.89	4.49	0.52
Carmichael et al.	1987	9	0.00	28.00	N/A	N/A	0	0	0	0	0	0	0	Blood	1.86	0.12	0.62	0.06
		9	100.00	27.50											2.58	0.20	0.94	0.08

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Table 1 (*continued*)

Authors	Year	*n*[a]	% female[b]	Age *M*	Time of day[c]	Fast[d]	Fast[e]	Eat[e]	Drink[e]	Caffeine[e]	Smoking[e]	Alcohol[e]	Exercise[e]	Specimen	Oxy *M*[f]	Oxy*SD*[f]	Oxy *M*log[g]	Oxy *SD*log[g]
Carson et al.	2012	17	35.30	35.47	10:00 am − 2:00 pm	N/A	0	0	0	0	0	0	0	Blood	263.10	103.40	5.50	0.38
Carter et al.	2007	8	0.00	N/A	N/A	N/A	0	0	0	0	0	0	0	Blood	175.00	23.08	5.16	0.13
		8	0.00											Saliva	1.52	0.80	0.30	0.49
Chang et al.	2014	82	54.88	34.69	N/A	N/A	0	0	0	0	0	0	0	Blood	26.26	5.87	3.24	0.22
Chicharro et al.	2001	10	0.00	23.00	8:00 am − 11:00 am	Yes	0	0	1	1	0	1	1	Blood	0.18	0.03	−1.73	0.17
		12	0.00	26.00											0.11	0.02	−2.22	0.18
Chiodera, Louis & Legros	1984	3	100.00	N/A	N/A	Yes	0	0	0	0	1	0	0	Blood	5.40	0.52	1.68	0.10
		6	0.00	N/A											5.10	0.73	1.62	0.14
Chiodera & Coiro	1991	7	0.00	N/A	9:00 am	Yes	1	0	0	0	0	0	0	Blood	2.57	0.20	0.94	0.08
		7	0.00	N/A											2.40	0.20	0.87	0.08
Chiodera & Coiro	1992	7	0.00	N/A	8:00 am	Yes	1	0	0	0	1	0	1	Blood	2.55	0.10	0.94	0.04
Chiodera et al.	1992	8	0.00	N/A	8:00 am	Yes	1	0	0	0	0	0	0	Blood	2.59	0.68	0.92	0.26
		8	0.00	N/A											2.90	0.37	1.06	0.13
Chiodera et al.	1995	7	0.00	N/A	8:00 am	Yes	1	0	0	0	0	0	0	Blood	2.52	0.26	0.92	0.10
Chiodera et al.	1996a	14	0.00	N/A	9:00 am	Yes	1	0	0	0	1	0	0	Blood	2.61	0.45	0.94	0.17
Chiodera et al.	1996b	6	0.00	N/A	8:30 am	Yes	1	0	0	0	1	0	1	Blood	2.43	0.86	0.83	0.34
Chiodera et al.	1998a	6	0.00	N/A	8:00 am	Yes	1	0	0	0	1	0	0	Blood	2.49	0.17	0.91	0.07
Chiodera et al.	1998b	7	0.00	N/A	8:30 am	Yes	1	0	0	0	0	0	1	Blood	2.32	0.53	0.82	0.23
Christensen et al.	2014	13	38.46	31.40	Morning	Yes	0	0	0	1	1	1	0	Blood	14.51	5.23	2.61	0.35
		13													95.11	90.25	4.23	0.80
		13													1.45	1.30	0.08	0.77
		13													3.27	2.63	0.94	0.71
Coiro & Chiodera	1991	7	0.00	N/A	8:30 am	Yes	1	0	0	0	0	0	1	Blood	2.19	0.45	0.76	0.20
Coiro et al.	1992	8	100.00	N/A	9:00 am	Yes	1	0	0	0	0	0	1	Blood	2.44	0.25	0.89	0.10
		8	100.00	N/A											2.37	0.28	0.86	0.12
Cong et al.	2015	19	0.00	35.60	1:09 pm	Yes	1	1	1	1	1	1	1	Saliva	41.25	25.74	3.56	0.57
Daubenbüchel et al.	2016	73	56.16	37.23	N/A	Yes	1	1	0	0	0	0	0	Saliva	5.55	3.82	1.52	0.62
Daughters et al.	2015	40	0.00	20.98	N/A	Yes	0	0	1	1	1	1	0	Saliva	77.93	74.46	4.03	0.80
		40	0.00	20.98											45.96	33.27	3.62	0.65
De Groot et al.	1995	6	0.00	33.17	N/A	No	0	0	0	0	0	0	0	Blood	1.23	0.25	0.19	0.20
de Jong et al.	2015	17	41.18	36.44	6:00 pm − 12:00 am	Yes	1	1	1	1	1	1	0	Saliva	1.55	0.29	0.42	0.18
		30	50.00	N/A	12:58 pm		1	1	1	1	0	1	1		1.42	0.19	0.34	0.13
Demitrack et al.	1990	11	100.00	25.50	9:00 am − 09:30 am	Yes	1	1	0	0	0	0	1	CSF	8.01	3.43	2.00	0.41
Ditzen et al.	2007	22	100.00	26.80	4:00 pm − 7:00 pm	Yes	1	1	0	1	1	1	1	Blood	10.05	7.04	2.30	0.15
		22	100.00	26.60											11.74	7.74	2.45	0.14
		17	100.00	25.70											9.22	7.34	2.20	0.19
Dolder et al.	2017	60	50.00	25.00	N/A	Yes	1	1	0	1	1	0	0	Blood	6.15	2.63	1.73	0.41
Domes et al.	2010	16	100.00	24.20	9:00 am − 6:00 pm	Yes	1	1	1	1	1	1	1	Blood	5.70	8.10	1.19	1.05
Dumont et al.	2009	15	20.00	21.10	10:25 am	No	0	0	0	0	0	0	0	Blood	0.81	1.16	−0.77	1.06
Eisenach, Tong & Curry	2015	20	60.00	37.00	Morning	Yes	1	1	1	1	0	1	0	CSF	9.50	3.10	2.20	0.32
Emeny et al.	2015	952	47.69	75.59	Morning	No	0	0	0	0	0	0	0	Blood	310.96	460.07	5.16	1.08
Engert et al.	2016	65	100	40.18	12:0 pm − 6:00 pm	No	0	0	0	0	0	0	0	Blood	0.47	0.08	−0.77	0.17
		49	0.00	40.18											0.37	0.07	−1.01	0.19
Fancourt et al.	2016	72	80.60	56.86	7:00 pm	N/A	0	0	0	0	0	0	0	Saliva	5.14	0.32	1.64	0.06
		66	81.60	59.69											5.15	0.35	1.64	0.07
Feldman, Samson & O'Dorisio	1988	7	25.00	31.00	N/A	Yes	1	1	0	0	0	0	0	Blood	171.00	47.62	5.10	0.27
Feldman et al.	2010	41	0.00	29.10	1:00 pm − 4:00 pm	N/A	0	0	0	0	0	0	0	Saliva	7.09	3.95	1.82	0.52
Feldman, Gordon & Zagoory-Sharon	2011	41	0.00	29.10	1:00 pm − 4:00 pm	N/A	0	0	0	0	0	0	0	Blood	405.10	151.88	5.94	0.36
		41	0.00	29.10										Saliva	7.09	2.24	1.91	0.33
		41	0.00	29.10										Urine	9.81	13.00	1.78	1.01
Feldman et al.	2012	121	0.00	N/A	4:00 pm − 7:00 pm	N/A	0	0	0	0	0	0	0	Blood	378.19	220.07	5.79	0.54
		80	50.00	N/A											318.82	171.04	5.63	0.50
Ferreira et al.	1998	17	100.00	34.40	9:00 am	Yes	1	1	0	1	1	1	0	Blood	10.88	4.43	2.31	0.39
		16	100.00	32.90											12.19	3.86	2.45	0.31
Fisher, Baylis & Frier	1987	6	0.00	24.00	N/A	Yes	1	1	1	1	1	1	1	Blood	0.71	0.24	−0.40	0.34

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Table 1 (*continued*)

Authors	Year	n[a]	% female[b]	Age M	Time of day[c]	Fast[d]	Fast[e]	Eat[e]	Drink[e]	Caffeine[e]	Smoking[e]	Alcohol[e]	Exercise[e]	Specimen	Oxy M[f]	OxySD[f]	Oxy Mlog[g]	Oxy SDlog[g]
Fisher et al.	1989	6	0.00	N/A	N/A	Yes	1	0	0	0	0	0	0	Blood	0.71	0.24	−0.40	0.34
Floyd, Pauley & Hesse	2010	50	100.00	26.83	N/A	N/A	0	0	0	0	0	0	0	Blood	268.48	293.94	5.20	0.89
		50	0.00	26.83											319.20	293.94	2.46	0.78
Forsling et al.	1998	15	0.00	25.00	5:00 pm	Yes	0	0	0	0	1	1	1	Blood	1.89	1.20	0.47	0.58
		9	0.00	70.00											3.69	1.65	1.21	0.43
Forsling, Wheeler & Williams	1999	8	0.00	21.00	2:30 pm	Yes	1	1	1	1	1	1	1	Blood	1.71	1.13	0.35	0.60
Forsling & Williams	2002	15	0.00	N/A	2:00 pm	Yes	0	0	0	0	1	1	1	Blood	2.36	1.28	0.73	0.51
Francis et al.	2016	10	20.00	25.80	9:00 am − 9:20 am	Yes	0	0	0	0	0	1	0	Urine	3.50	2.00	1.11	0.53
Frank et al.	2000	17	100	23.40	N/A	N/A	0	0	0	0	0	0	0	CSF	6.31	1.96	1.80	0.30
Frijling et al.	2015	20	0.00	41.40	9:30 am − 7:00 pm	Yes	1	1	1	1	1	1	1	Saliva	3.00	3.54	0.66	0.93
		19	100.00	38.40											2.42	3.77	0.27	1.11
Fruhstorfer et al.	1988	7	0.00	N/A	8:00 am	Yes	0	0	0	1	1	1	0	Blood	0.82	2.20	−1.25	1.45
Fujiwara et al.	2012	50	100.00	35.90	11:00 am − 2:00 pm	N/A	0	0	0	0	0	0	0	Urine	181.50	63.67	5.14	0.34
		31	0.00	36.90											188.00	70.17	5.17	0.36
Gerra et al.	2017	18	0.00	33.20	8:00 am	Yes	0	0	0	1	1	0	0	Blood	252.70	89.70	5.47	0.34
Glovinsky et al.	1994	15	33.33	30.00	9:00 am	N/A	0	0	0	0	0	0	0	CSF	8.92	3.01	2.13	0.33
Goldman et al.	2008	5	42.86	34.70	7:30 pm	No	0	0	0	0	0	0	0	Blood	240.00	224.00	5.17	0.79
Gordon et al.	2008	45	53.30	24.63	4:30 pm − 6:30 pm	Yes	1	1	0	1	0	1	0	Blood	258.76	257.66	5.21	0.83
Gordon et al.	2010a	76	0.00	29.45	4:00 pm − 8:00 pm	Yes	1	1	0	0	0	0	0	Blood	401.98	360.28	5.70	0.77
Gordon et al.	2010b	43	0.00	28.08	4:00 pm − 8:00 pm	Yes	1	1	0	0	0	0	0	Blood	370.59	255.54	5.72	0.62
Gordon et al.	2010c	37	0.00	28.81	4:00 pm − 8:00 pm	Yes	1	1	0	0	0	0	0	Blood	306.01	181.14	5.57	0.55
Gossen et al.	2012	8	0.00	26.40	1:00 pm − 7:00 pm	Yes	1	1	1	1	1	1	0	Blood	1.70	2.49	−0.04	1.07
Gouin et al.	2010	74	50.00	38.47	7:45 am	Yes	0	0	0	0	1	0	0	Blood	308.26	226.28	5.15	0.66
Gouin, Pournajafi-Nazarloo & Carter	2015	59	47.50	23.81	9:30 am − 12:30 pm	Yes	1	1	0	1	0	0	0	Blood	234.24	60.21	5.42	0.25
Graugaard-Jensen et al.	2014	22	0.00	25.60	8:00 am	Yes	0	0	1	1	1	1	1	Blood	2.25	0.66	0.77	0.29
		15	100.00	25.50											1.98	0.97	0.58	0.64
Grenbäck, Hulting & Petersson	2007	4	0.00	47.74	Morning	Yes	1	0	0	0	0	0	0	Blood	13.85	6.38	2.53	0.44
		9	100.00	57.11											13.09	5.19	2.50	0.38
Grewen et al.	2005	38	0.00	29.26	N/A	N/A	0	0	0	0	0	0	0	Blood	1.53	1.17	0.19	0.68
		38	100.00	27.66											1.65	1.23	0.28	0.67
Grewen et al.	2008	25	100.00	27.40	12:00 pm − 2:00 pm	Yes	0	0	0	0	1	0	0	Blood	3.90	2.75	1.16	0.64
		23	100.00	27.40											7.05	4.08	1.81	0.54
Handlin et al.	2011	10	100.00	53.00	evening (most)	N/A	0	0	0	0	0	0	0	Blood	169.71	110.21	4.96	0.59
		10	100.00	42.00											210.10	197.48	5.03	0.80
Handlin et al.	2012	10	100.00	53.00	N/A	N/A	0	0	0	0	0	0	0	Blood	169.71	110.29	4.96	0.59
Heim et al.	2009	8	100.00	31.30	4:00 pm	Yes	1	1	1	1	1	1	1	CSF	12.32	3.71	2.51	0.11
		14	100.00	31.30											17.15	3.55	2.84	0.06
Hermann et al.	1993	21	56.00	29.00	N/A	N/A	0	0	0	0	0	0	0	Blood	26.24	8.25	3.22	0.31
Hew-Butler et al.	2008	82	29.00	43.00	6:30 am − 8:30 am	N/A	0	0	0	0	0	0	0	Blood	1.87	0.97	0.51	0.49
Higashida et al.	2012	101	N/A	N/A	2:00 pm − 5:00 pm	Yes	1	1	1	1	0	1	0	Blood	198.20	24.70	4.82	0.97
Hoge et al.	2008	20	45.00	35.50	8:15 am	N/A	0	0	0	0	0	0	0	Blood	145.00	52.90	4.91	0.35
Hoge et al.	2012	27	37.04	40.00	1:00 pm − 4:00 pm	N/A	0	0	0	0	0	0	0	Blood	354.00	181.00	5.75	0.48
Hogenelst et al.	2016	40	50.00	22.10	9:00 am − 2:30 pm	Yes	1	1	0	0	0	1	0	Blood	2.07	0.66	0.68	0.31
Holbrook, Hahn-Holbrook & Holt-Lunstad	2015	34	55.90	21.82	9:30 am − 5:30 pm	No	0	0	0	0	0	0	0	Saliva	6.07	2.56	1.72	0.41
Honer et al.	1986	6	0.00	28.00	9:00 am − 9:45 am	Yes	1	0	0	0	0	0	0	Blood	1.44	0.71	0.26	0.47
Imamura et al.	2016	198	100.00	74.80	9:00 am − 3:00 pm	No	0	0	0	0	0	0	0	Blood	140.00	133.00	4.62	0.80
		119	0.00	73.90											50.00	38.00	3.68	0.68
Jaeggi et al.	2015	31	0.00	37.80	5:50am − 11:30 am	No	0	0	0	0	0	0	0	Saliva	30.24	18.11	3.26	0.55
Jansen et al.	2006	14	7.14	21.00	10:00 am − 4:00 pm	Yes	1	1	1	1	1	1	1	Blood	7.51	8.87	1.97	0.31
Javor et al.	2014	30	0.00	26.67	9:00 am − 13:00 pm	Yes	1	1	1	1	1	1	0	Saliva	18.77	9.62	2.82	0.48
		30	0.00	26.67										Blood	32.45	19.50	3.33	0.56
Jobst et al.	2014a	21	100.00	N/A	8:00 am − 11:00 am	N/A	0	0	0	0	0	0	0	Blood	447.00	214.38	6.10	0.10
Jobst et al.	2014b	45	0.00	24.60	8:00 am − 9:00 am	N/A	0	0	0	0	0	0	0	Blood	376.00	229.91	5.77	0.56

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Table 1 (*continued*)

Authors	Year	n[a]	% female[b]	Age M	Time of day[c]	Fast[d]	Fast[e]	Eat[e]	Drink[e]	Caffeine[e]	Smoking[e]	Alcohol[e]	Exercise[e]	Specimen	Oxy M[f]	OxySD[f]	Oxy Mlog[g]	Oxy SDlog[g]
Jobst et al.	2015	19	31.58	46.58	8:00 am – 11:00 am	Yes	1	1	1	1	1	1	0	Blood	518.58	236.64	6.25	0.10
John	2014	72	69.40	19.34	N/A	N/A	0	0	0	0	0	0	0	Saliva	2.39	0.89	0.81	0.36
		116	60.30	19.34											2.73	1.11	0.93	0.39
		95	65.30	19.82											2.31	0.95	0.76	0.40
Johnson et al.	1990a	6	100.00	N/A	N/A	Yes	0	0	0	1	1	1	0	Blood	1.11	0.24	0.08	0.22
Johnson et al.	1990b	6	100.00	N/A	N/A	Yes	0	0	0	1	1	1	1	Blood	0.99	0.64	−0.18	0.59
		6	100.00	N/A											1.04	0.71	−0.15	0.62
Jokinen et al.	2012	19	36.84	30.00	7:45 am – 8:45 am	Yes	1	0	0	0	0	0	0	Blood	4.90	3.80	1.35	0.69
		18	36.98	30.00	8:00 am – 9:00 am									CSF	19.20	15.10	2.71	0.69
Kacheva et al.	2014	4	50.00	40.30	N/A	N/A	0	0	0	0	0	0	0	Blood	13.80	1.70	2.62	0.12
Katsarou	2016	7	28.57	50.14	Morning	Yes	0	0	0	1	1	0	0	Saliva	8.14	6.62	1.84	0.71
Keeler et al.	2015	4	50.00	N/A	4:00 pm – 5:00 pm	Yes	1	1	1	1	1	1	1	Blood	201.80	104.20	5.19	0.49
Kirkpatrick et al.	2014	12	14.29	25.40	9:20 am	Yes	1	1	0	0	1	1	0	Urine	18.84	15.85	2.67	0.73
Kling et al.	1994	6	33.33	35.30	30 h	N/A	0	0	0	0	0	0	0	CSF	3.80	0.98	1.30	0.25
Koch et al.	1990	6	66.67	N/A	12:00 pm – 2:00 pm	Yes	1	0	0	0	0	0	0	Blood	24.30	11.20	3.09	0.43
		6	66.67	N/A											17.00	5.70	2.78	0.33
Kostoglou-Athanassiou et al.	1996	8	100.00	N/A	5:00 pm	Yes	0	0	0	0	1	1	1	Blood	2.50	0.93	0.85	0.36
Kostoglou-Athanassiou et al.	1998a	10	0.00	N/A	5:00 pm	Yes	0	0	0	0	0	1	1	Blood	6.31	4.59	1.63	0.65
		12	0.00	N/A											7.03	3.95	1.75	0.63
Kostoglou-Athanassiou et al.	1998b	8	100.00	N/A	20 h	Yes	0	0	0	0	1	1	1	Blood	4.23	1.13	1.41	0.26
		7	100.00	N/A											5.44	1.06	1.68	0.19
Kreutz	2014	24	76.19	N/A	N/A	N/A	0	0	0	0	0	0	0	Saliva	13.04	5.59	2.48	0.41
Krüger et al.	2003	10	0.00	25.20	N/A	N/A	0	0	0	0	0	0	0	Blood	76.03	31.84	4.25	0.40
Krüger et al.	2006	10	0.00	27.00	5:45 pm	N/A	0	0	0	0	0	0	0	CSF	7.72	1.14	2.03	0.15
		10	0.00	28.50											8.52	2.31	2.11	0.27
Kujath et al.	2015	74	100.00	28.40	N/A	No	0	0	0	0	0	0	0	Blood	346.20	324.20	5.53	0.79
Kumaresan et al.	1983	11	100.00	24.00	9:00 am – 10:00 am	N/A	0	0	0	0	0	0	0	Blood	3.12	6.90	0.25	1.33
Laczi et al.	1998	6	100.00	N/A	8:00 am	Yes	1	0	1	1	0	1	0	Blood	5.20	1.94	1.58	0.36
Lancaster et al.	2015	37	0.00	23.69	10:00 am – 11:00 am	N/A	0	0	0	0	0	0	0	Blood	307.28	122.61	5.65	0.38
Landgraf	1985	3	0.00	26.67	10:00 am – 12:00 pm	Yes	1	1	1	1	1	1	1	Blood	4.12	0.49	1.41	0.12
Lawson et al.	2011	19	100.00	27.50	12 h	Yes	1	1	1	1	0	1	1	Blood	32.03	22.40	3.27	0.63
Lawson et al.	2012	13	100.00	22.00	9:00 am	Yes	1	1	1	1	1	1	0	Blood	16.40	8.29	2.68	0.48
Le Mellédo et al.	2001	12	100.00	27.00	N/A	N/A	0	0	0	0	0	0	0	Blood	1.28	0.37	0.21	0.28
Leake, Weitzman & Fisher	1980	6	0.00	N/A	N/A	N/A	0	0	0	0	0	0	0	Blood	1.33	0.81	0.13	0.56
		6	100.00	N/A											1.33	0.42	0.24	0.31
Leake, Buster & Fisher	1984	9	100.00	N/A	10:00 am – 2:00 pm	N/A	0	0	0	0	0	0	0	Blood	2.00	0.99	0.58	0.47
		5	0.00	N/A											2.17	0.38	0.76	0.17
Legros et al.	1984	6	0.00	N/A	9:30 am	Yes	1	0	0	0	0	0	0	Blood	6.52	3.62	1.74	0.52
Lien et al.	2016	96	57.29	N/A	N/A	N/A	0	0	0	0	0	0	0	Blood	28.40	14.00	3.24	0.47
Light et al.	2005	19	100.00	51.70	N/A	Yes	0	0	0	1	0	0	0	Blood	1.36	0.57	0.23	0.40
		19	100.00	49.60											1.37	0.57	0.24	0.40
		16	100.00	54.10											2.22	0.76	0.74	0.33
Lischke et al.	2012a	23	0.00	25.78	N/A	Yes	1	1	1	1	1	1	1	Blood	24.63	18.97	2.97	0.68
		24	0.00	26.38											27.18	16.61	3.14	0.56
Lui et al.	2010	20	0.00	30.50	N/A	N/A	0	0	0	0	0	0	0	Blood	79.30	17.13	4.35	0.21
Marazziti et al.	2006	45	73.33	31.50	8:00 am – 9:00 am	Yes	1	0	0	0	0	0	0	Blood	1.53	1.18	0.19	0.68
Marazziti et al.	2012	20	60.00	35.00	8:00 am – 9:00 am	Yes	1	1	1	1	0	1	0	Blood	1.14	1.07	−0.18	0.79
Marazziti	2015a	44	47.73	28.30	8:00 am – 9:00 am	Yes	1	0	0	0	0	0	0	Blood	2.55	2.18	0.66	0.74
Marchesi et al.	1997	9	0.00	43.70	8:30 am	Yes	1	1	1	1	1	1	1	Blood	2.24	0.15	0.80	0.07
Marsh et al.	2015	37	60.27	22.31	N/A	N/A	0	0	0	0	0	0	0	Saliva	2.15	0.36	0.75	0.17
		35	60.27	22.31											0.86	0.13	−0.16	0.15

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Table 1 (*continued*)

Authors	Year	n[a]	% female[b]	Age M	Time of day[c]	Fast[d]	Fast[e]	Eat[e]	Drink[e]	Caffeine[e]	Smoking[e]	Alcohol[e]	Exercise[e]	Specimen	Oxy M[f]	OxySD[f]	Oxy Mlog[g]	Oxy SDlog[g]
Martin et al.	1998	6	100.00	25.00	8:00 am – 10:00 am	Yes	1	0	0	0	0	0	1	CSF	5.14	0.91	1.62	0.18
Mascaro, Hackett & Riling	2014	83	0.00	33.20	7:30 am – 3:25 pm	No	0	0	0	0	0	0	0	Blood	8.80	4.35	2.07	0.47
		48	0.00	30.40											6.60	3.47	1.77	0.49
McQuaid et al.	2016	67	100.00	19.37	1:00 pm – 5:30 pm	Yes	1	1	1	1	1	1	0	Blood	11.20	4.75	2.33	0.41
Mennella & Pepino	2006	8	100.00	25.00	8:45 am	Yes	1	0	0	0	1	0	0	Blood	19.03	8.23	2.86	0.41
Miaskiewicz, Stricker & Verbalis	1989	14	7.14	N/A	N/A	Yes	1	0	0	0	1	1	0	Blood	2.68	0.90	0.93	0.33
Miller et al.	2009	10	100.00	35.90	Afternoon or early evening	N/A	0	0	0	0	0	0	0	Blood	33.50	37.30	3.11	0.90
		10	0.00	38.30											77.70	93.00	3.91	0.94
Mitchell et al.	1981	6	100.00	N/A	N/A	N/A	0	0	0	0	0	0	0	Blood	13.32	2.47	2.57	0.18
Mitchell et al.	2013	21	0.00	44.95	N/A	N/A	0	0	0	0	0	0	0	Urine	5.78	2.38	1.67	0.40
Mohiyeddini, Opacka-Juffry & Gross	2014	90	0.00	27.70	N/A	N/A	0	0	0	0	0	0	0	Blood	366.22	2150.76	4.12	1.89
Mohiyeddini & Opacka-Juffry	2015	73	0.00	28.00	2:00 pm – 5:00 pm	Yes	1	1	1	1	1	1	0	Blood	380.00	24.60	5.94	0.06
Monde	2014	15	66.60	30.47	12:00 pm – 5:00 pm	Yes	1	1	1	1	1	1	0	Saliva	4.26	4.03	1.42	0.24
		53	38.18	18.00	1:00 pm – 5:00 pm										6.56	4.00	1.88	0.08
Monteleone et al.	2016	19	100.00	27.70	N/A	Yes	1	0	0	0	0	0	0	Blood	21.39	7.94	3.00	0.36
Montgomery et al.	1991	9	0.00	N/A	4:00 am	Yes	0	0	0	0	1	1	1	Blood	8.67	1.50	2.15	0.17
Moons, Way & Taylor	2014	55	65.45	21.00	N/A	N/A	0	0	0	0	0	0	0	Blood	5.26	0.52	1.66	0.10
		104	58.65	21.00											5.43	0.54	1.69	0.09
Morhenn, Beavin & Zak	2012	65	52.30	21.36	N/A	N/A	0	0	0	0	0	0	0	Blood	190.37	122.04	5.08	0.59
		30	53.30	21.36											249.93	173.51	5.32	0.63
Motoki et al.	2016	27	0.00	20.63	2:00 pm – 5:00 pm	Yes	1	1	0	1	1	1	1	Blood	21.77	7.25	3.03	0.32
		24	100.00	20.17											20.01	3.93	2.98	0.19
Munro et al.	2013	15	100.00	21.70	10:00 am – 3:00 pm	Yes	0	0	0	0	1	1	0	Blood	183.60	77.50	5.13	0.40
Murphy et al.	1987	13	0.00	N/A	10:30 am	Yes	0	0	0	0	1	1	1	Blood	1.41	1.80	0.11	0.68
Murphy et al.	1990	8	0.00	N/A	2:30 pm	Yes	0	0	0	0	1	1	1	Blood	1.11	0.57	−0.01	0.48
Nagasawa et al.	2015	20	80.00	36.60	N/A	Yes	1	1	1	1	0	1	0	Urine	20.10	25.66	2.52	0.98
		8	87.50	36.60											12.10	13.30	2.10	0.89
		11	45.45	N/A											20.62	5.21	3.00	0.25
Newman et al.	1999	8	0.00	24.97	9:00 am	Yes	1	1	1	1	1	1	1	Blood	10.78	41.01	1.01	1.66
		6	0.00	61.42											5.90	4.92	1.51	0.73
		7	100.00	27.86											10.07	28.42	1.21	1.48
		9	100.00	58.56											13.31	30.30	1.68	1.35
North	1991	25	40.00	N/A	9:00 am – 11:00 am	Yes	1	1	1	1	1	1	1	Blood	2.25	1.70	0.59	0.67
Nussey et al.	1986	10	40.00	N/A	8:00 am – 11:00 am	Yes	1	0	1	1	1	1	0	Blood	1.15	0.63	0.01	0.51
Nussey et al.	1988a	9	55.56	N/A	N/A	N/A	0	0	0	0	0	0	0	Blood	1.61	1.20	0.26	0.66
Nussey et al.	1988b	6	0.00	1.91	N/A	Yes	1	0	0	0	0	0	0	Blood	1.91	2.47	0.15	0.99
Ohlsson et al.	2002	8	100.00	37.00	8:00 am	Yes	1	1	1	1	1	1	0	Blood	1.01	0.30	−0.03	0.29
Ohlsson, Rehfeld & Forsling	2004	11	100.00	34.40	Morning	Yes	1	0	0	0	1	0	0	Blood	1.31	0.33	0.24	0.25
Opacka-Juffry & Mohiyeddini	2012	90	0.00	27.70	2:00 pm – 5:00 pm	Yes	1	1	1	1	0	1	0	Blood	377.60	226.74	5.78	0.55
Ottesen et al.	1988	6	100.00	N/A	N/A	No	0	0	0	0	0	0	0	Blood	2.40	0.69	0.84	0.28
Ozsoy, Esel & Kula	2009	32	62.50	39.78	8:00 am	Yes	1	0	0	0	0	0	0	Blood	13.11	7.54	2.45	0.49
Park	2007	51	100.00	22.30	10:00 am	No	0	0	0	0	0	0	0	Blood	235.60	114.20	5.36	0.46
		45	0.00	22.30											179.50	159.40	4.90	0.76
Parker et al.	2010	19	47.37	34.26	6:00 pm	No	0	0	0	0	0	0	0	Blood	0.96	0.31	−0.04	0.07
Peskind et al.	1987	7	0.00	25.90	1:00 am – 3:00 pm	Yes	0	0	0	1	1	0	1	Blood	2.22	1.69	0.57	0.68
		7	0.00	25.90										CSF	10.29	1.83	2.32	0.18
Pitts et al.	1995	18	50.00	N/A	4:00 pm	Yes	0	0	0	0	0	0	1	CSF	13.86	6.92	2.52	0.47
Prehn et al.	2013	23	0.00	25.78	9:00 am – 6:00 pm	Yes	1	1	1	1	1	1	1	Blood	24.60	19.00	2.97	0.68
		24	0.00	26.38											27.20	16.60	3.14	0.56
Quintana et al.	2015	16	0.00	23.81	Throughout the day	No	0	0	0	0	0	0	0	Blood	6.07	5.88	1.47	0.81
Radant et al.	1992	7	0.00	28.00	9:30 am	Yes	1	0	0	0	1	1	0	Blood	2.22	2.65	0.79	0.12
		4	0.00	26.00											2.93	0.72	1.05	0.24

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Table 1 (*continued*)

Authors	Year	*n*[a]	% female[b]	Age *M*	Time of day[c]	Fast[d]	Fast[e]	Eat[e]	Drink[e]	Caffeine[e]	Smoking[e]	Alcohol[e]	Exercise[e]	Specimen	Oxy *M*[f]	Oxy*SD*[f]	Oxy *M*log[g]	Oxy *SD*log[g]
Rapaport, Schetter & Bresee	2010	24	59.00	30.70	3:00 pm − 7:00 pm	Yes	0	0	0	1	1	1	1	Blood	188.39	101.96	5.11	0.51
		22	50.00	33.30											218.30	165.11	5.16	0.67
Raskind et al.	1986	7	0.00	68.00	Early afternoon	Yes	0	0	1	1	1	1	0	CSF	17.89	2.65	2.87	0.15
		8	0.00	25.00											16.66	3.17	2.80	0.19
ReYes	2014	44	0.00	25.02	10:00 am − 2:00 pm	N/A	0	0	0	0	0	0	0	Blood	32.48	8.56	3.45	0.26
Rubin et al.	2010	31	100.00	27.05	55% in the afternoon	N/A	0	0	0	0	0	0	0	Blood	322.93	187.05	5.63	0.54
		27	0.00	27.93											293.19	210.46	5.47	0.64
Rubin et al.	2013	14	100.00	28.43	N/A	N/A	0	0	0	0	0	0	0	Blood	342.98	217.30	5.67	0.58
		24	0.00	27.58											427.28	259.01	5.90	0.56
Rubin et al.	2014	66	57.58	37.18	At least 87% before noon	N/A	0	0	0	0	0	0	0	Blood	5.94	0.89	1.77	0.15
		61	75.41	42.77											5.72	0.86	1.73	0.15
		43	67.44	39.79											5.69	0.85	1.73	0.15
		91	64.84	41.01											5.86	1.05	1.75	0.18
Rubin et al.	2017	36	100.00	34.67	N/A	N/A	0	0	0	0	0	0	0	Blood	6.15	0.89	1.81	0.14
		24	0.00	36.96											6.10	0.66	1.80	0.11
Saito et al.	2014	12	0.00	26.08	2:00 pm − 6:00 pm	Yes	1	1	1	0	0	1	1	Urine	344.38	196.18	5.70	0.53
Salonia et al.	2005	20	100.00	33.80	8:00 am − 10:00 am	Yes	0	0	0	0	1	0	0	Blood	2.41	1.12	0.78	0.44
		10	100.00	32.40											1.98	0.79	0.61	0.39
Sanders, Freilicher & Lightman	1990	10	100.00	29.40	N/A	N/A	0	0	0	0	0	00	0	Blood	2.97	5.76	0.31	1.25
		10	100.00	26.10											1.37	1.01	0.10	0.66
		10	0.00	32.60											1.05	0.44	−0.03	0.40
		10	0.00	30.90											1.74	1.52	0.30	0.72
		10	100.00	24.00											1.22	0.38	0.15	0.30
		10	100.00	26.80											1.24	0.41	0.16	0.32
		21	100.00	23.20											1.96	1.37	0.47	0.63
		21	100.00	22.30											1.92	0.78	0.58	0.39
Schneiderman et al.	2012	53	100.00	22.84	Mid-afternoon hours	N/A	0	0	0	0	0		0	Blood	509.83	228.67	6.14	0.43
		60	0.00	25.03											480.76	219.28	6.08	0.43
		23	100.00	24.63											263.76	240.68	5.27	0.78
		20	0.00	24.63											250.98	245.10	5.19	0.82
Schneiderman et al.	2014	60	100.00	22.84	Mid-afternoon hours	Yes	1	1	0	0	0	0	0	Blood	459.05	140.26	6.08	0.30
		60	0.00	25.03											459.05	140.26	6.08	0.30
		40	52.50	24.63											257.82	239.92	5.24	0.79
Seckl et al.	1988a	9	0.00	N/A	N/A	Yes	0	0	0	1	1	1	0	Blood	1.91	0.30	0.63	0.16
Seckl et al.	1988b	6	0.00	N/A	N/A	Yes	1	1	0	1	1	1	0	Blood	1.51	0.73	0.31	0.46
Seckl, Johnson & Lightman	1989	6	0.00	N/A	N/A	Yes	0	0	0	1	1	1	0	Blood	1.18	0.88	−0.06	0.67
Shukovski, Healy & Findlay	1989	4	100.00	N/A	N/A	N/A	0	0	0	0	0	0	0	Blood	10.78	7.96	2.20	0.60
Silber et al.	1987	20	100.00	28.00	Morning	Yes	1	0	0	0	0	0	0	Blood	10.20	5.19	2.21	0.48
Silber, Larsson & Uvnäs-Moberg	1991	20	100.00	26.40	Morning	Yes	1	0	0	0	0	0	0	Blood	14.16	2.68	2.63	0.19
		20	100.00	28.00											16.22	6.45	2.71	0.38
Smith et al.	2013	180	0.00	29.30	Early evening; some late afternoon	Yes	0	0	0	1	1	1	0	CSF	2.02	1.56	0.47	0.68
		180	100.00	27.90											1.92	1.67	0.37	0.75
Steinwall et al.	1998	8	100.00	N/A	7:00 am − 9:00 am	N/A	0	0	0	0	0	0	0	Blood	2.63	1.10	0.89	0.40
Stock et al.	1989	9	77.77	35.00	N/A	Yes	1	0	0	0	0	0	0	Blood	27.00	30.00	2.89	0.90
Stock, Silber & Uvnäs-Moberg	1989	20	100.00	N/A	Morning	Yes	1	0	0	0	0	0	0	Blood	10.00	2.52	2.27	0.25
Stock, Bremme, Uvnäs-Moberg	1991	15	100.00	N/A	N/A	Yes	1	0	0	0	0	0	0	Blood	12.00	7.67	2.31	0.59
Stock, Karlsson & von Schoultz	1994	5	100.00	25.40	10:00 pm	Yes	1	0	0	0	0		0	Blood	31.00	8.25	3.40	0.26
Strauss et al.	2015b	22	31.82	43.14	9:00 am − 5:00 pm	No	0	0	0	0	0	0	0	Blood	19.66	5.86	2.94	0.29
Tabak et al.	2011	35	100.00	19.26	6:00 pm − 7:30 pm	Yes	1	1	1	1	0	1	1	Blood	1.61	2.78	−0.21	1.18
Taylor, Saphire-Bernstein & Seeman	2010	32	0.00	21.60	Mid-afternoon	N/A	0	0	0	0	0	0	0	Blood	273.45	234.36	5.34	0.74
		53	100.00	21.60											248.75	180.01	5.31	0.65

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Table 1 (*continued*)

Authors	Year	*n*[a]	% female[b]	Age *M*	Time of day[c]	Fast[d]	Fast[e]	Eat[e]	Drink[e]	Caffeine[e]	Smoking[e]	Alcohol[e]	Exercise[e]	Specimen	Oxy *M*[f]	Oxy*SD*[f]	Oxy *M*log[g]	Oxy *SD*log[g]
Tops et al.	2013	57	100.00	20.51	12:00 pm − 3:00 pm	Yes	0	0	0	1	1	1	1	Saliva	8.18	5.36	1.92	0.60
Tseng et al.	2014	41	0.00	33.50	8:00 am − 10:00 am	Yes	1	0	0	0	0	0	0	Blood	26.14	6.13	3.24	0.23
		55	100.00	33.54											25.37	5.69	3.21	0.22
Turan et al.	2013	24	41.67	34.42	8:00 am − 9:00 am	Yes	0	0	0	0	0	1	0	Blood	108.59	65.70	4.53	0.56
Turner et al.	1999	25	100.00	28.12	9:15 am	Yes	1	0	0	0	0	1	0	Blood	4.61	0.27	1.53	0.06
Turner et al.	2002	32	100.00	N/A	8:00 am	N/A	0	0	0	0	0	0	0	Blood	3.16	3.95	0.68	0.97
Ückert et al.	2003	12	0.00	26.00	afternoon	Yes	0	0	0	1	0	0	1	Blood	71.10	41.20	4.12	0.54
Ulmer-Yaniv et al.	2016	46	50.00	N/A	3:00 pm − 8:00 pm	N/A	0	0	0	0	0	0	0	Blood	529.41	300.27	6.13	0.53
		32	51.43	N/A											250.58	91.12	5.46	0.35
Uvnäs-Moberg et al.	1989	18	100.00	38.00	8:00 am	Yes	1	1	0	0	1	0	0	Blood	9.06	7.64	1.94	0.73
Uvnäs-Moberg et al.	1991	10	N/A	N/A	N/A	Yes	1	0	0	0	0	0	0	Blood	16.42	10.66	2.62	0.59
van IJzendoorn et al.	2012	18	100.00	19.77	9:00 am	Yes	0	0	0	1	1	1	1	Saliva	2.44	2.46	0.54	0.84
		10	100.00	19.77											2.60	2.59	0.61	0.83
		18	100.00	19.77											2.77	2.76	0.67	0.83
van Londen et al.	1997	30	54.05	41.20	8:00 am	Yes	0	0	0	0	1	1	1	Blood	1.28	3.12	−0.72	1.39
Varga & Kekecs	2014	12	0.00	29.62	11:00 am − 3:30 pm	Yes	1	1	1	1	1	1	1	Saliva	1.97	2.14	0.29	0.88
		4	0.00	N/A											3.03	1.84	0.95	0.56
Walss-Bass et al.	2013	20	30.00	39.65	Morning	Yes	1	1	1	1	0	1	0	Blood	199.33	119.42	5.14	0.55
Weisman et al.	2012	35	0.00	29.70	1:00 pm − 5:00 pm	Yes	1	1	0	1	1	1	0	Saliva	20.91	22.84	2.65	0.89
Weisman et al.	2013	192	0.00	27.50	1:00 pm − 7:00 pm	N/A	0	0	0	0	0	0	0	Blood	399.91	183.65	5.90	0.44
Williams et al.	1985	4	100.00	N/A	9:00 am	N/A	0	0	0	0	0	0	0	Blood	1.01	0.20	−0.01	0.20
Williams et al.	1986	5	0.00	N/A	N/A	Yes	1	0	0	0	0	0	1	Blood	1.61	0.67	0.40	0.40
		6	66.67	N/A	N/A	N/A	0	0	0	0	0	0	0		1.63	1.32	0.24	0.71
Wolff et al.	2006	29	43.30	25.00	N/A	N/A	0	0	0	0	0	0	0	Blood	2.11	1.18	0.61	0.52
Zhong et al.	2010	1135	50.40	21.10	N/A	N/A	0	0	0	0	0	0	0	Blood	214.00	230.00	4.98	0.88

Note. The table shows the data basis for the meta-regressions. As some studies reported data separately for different subsamples, those were analyzed separately, as well, in order to include as many participants as possible into the meta-analytic procedure. N/A indicates that the information was not extractable from the paper.

[a] Number of participants of whom valid oxytocin values were available. If outliers were removed by primary study authors, they were not included into the present analysis, either.

[b] Percentage of female participants per sample.

[c] If a time period was reported instead of a timepoint, the mean was used for the meta-regressions, if the period did not exceed 6 h. If it exceeded 6 h, this information was considered as too imprecise and treated as missing. 12 am indicates midnight and 12 pm noon.

[d] Indicates whether any fasting instructions were given to the participants (Yes or no).

[e] Indicates whether we considered that participants were (1) or were not (0) instructed to refrain from eating, drinking, consuming caffeine, smoking, consuming alcohol, exercising, or from any of those behaviors ("fast"). Missing values in the fasting variables were imputed to 0, assuming that if no instructions were reported in the paper, they were presumably not given.

[f] Values represent pg/ml. [g] Values represent log-scaled pg/ml and were transformed according to the formulas provided in supplementary material 1.

Table 2
Baseline regression model.

Predictor	β (*SEM*)	*t*	*p*	CI
Intercept	5.62 (0.31)	18.38	< 0.01	5.02: 6.22
Year	0.34 (0.09)	3.74	< 0.01	0.16; 0.51
Risk of bias	−0.00 (0.01)	−0.41	0.68	−0.03; 0.02
SEM	−2.30 (0.27)	−8.37	< 0.01	−2.84; −1.76
Specimen				
Saliva	−4.03 (0.07)	−58.35	< 0.01	−4.16; −3.89
Urine	−1.76 (1.18)	−1.49	0.14	−4.09; 0.57
CSF	−2.77 (0.79)	−3.50	< 0.01	−4.32; −1.21
Extraction	−4.06 (0.10)	−42.45	< 0.01	−4.25; −3.89
Extraction*Specimen				
Extraction*Saliva	3.61 (0.14)	25.49	< 0.01	3.34; 3.89
Extraction*Urine	2.78 (1.19)	2.34	0.02	0.45; 5.12
Extraction*CSF	4.06 (0.80)	5.08	< 0.01	2.49; 5.63

Note. The model is based on 339 subsamples. Study- and assay-related heterogeneity were considered as variance components. Sample-level regressors: year (reference: 2 000 years AD, scale: 10 years), risk of bias and appropriateness score (0–30 points), *SEM* of oxytocin value reported in the primary study in order to adjust for bias using the PET-PEESE method (Stanley and Doucouliagos, 2014), specimen (reference: blood) and extraction (reference: unextracted samples). CI = confidence interval. CSF = cerebrospinal fluid.

each sample, as well as time of sampling, fasting instructions, specimen and oxytocin concentrations.

As comprehensive information was extracted from all 326 primary studies, the remaining results of the qualitative analyses are presented as supplementary information. Supplementary material 3 reports study type, sample overlaps, location of data collection, as well as number of participants, sex distribution, and age. It also shows the time of sampling, fasting instructions and specimen. The results of our risk of bias and appropriateness ratings for all 326 studies are shown in supplementary material 4.

3.3. Confounders of basal endogenous oxytocin concentrations

3.3.1. Baseline regression model

The results of the baseline regression model are shown in Table 2 and illustrated in Fig. 2.

There were significant differences in predicted oxytocin concentrations between specimens. In addition, there was a significant main effect of extraction, as well as significant interactive effects of specimen and extraction. The intercept represents the predicted mean oxytocin concentration within unextracted blood samples. It indicates that within unextracted blood samples, oxytocin was 275.61 pg/ml, as determined by the factor exp (5.62). Within extracted blood samples, mean predicted oxytocin was only 4.75 pg/ml. Within unextracted saliva samples, mean predicted oxytocin was 4.92 pg/ml and within extracted saliva samples, it was 3.15 pg/ml. Within unextracted urine samples, mean predicted oxytocin was 47.42 pg/ml and within extracted urine samples, it was 13.20 pg/ml. Mean predicted oxytocin was 17.31 pg/ml within unextracted CSF samples and within extracted CSF samples, it was 17.29 pg/ml. Our Open Science Framework repository contains the exact calculations of predicted oxytocin concentrations.

3.3.2. Impact of confounders

Table 3 shows the results of the subsequent inclusion of the potentially confounding variables in the regression model, across all studies. With increasing percentages of females and mean age of the samples, reported oxytocin concentrations also increased significantly. A significant impact of time of day was detected. Instructions to refrain from smoking prior to sample collection also led to significantly higher oxytocin concentrations. Instructions to refrain from eating, drinking, caffeine or alcohol consumption, exercising, as well as the combined fasting variable (i.e., considering any of the fasting instructions) did not exert a significant effect.

3.3.3. Subgroup analyses within studies using unextracted and extracted samples

The differential impact of confounders within studies using unextracted and extracted samples is also shown in Table 3. The effect of sex was replicated within unextracted and extracted samples, respectively. The effect of age was no longer significant in neither of the subgroups, which might be explained by the reduced statistical power and indicate that this effect was relatively small. The effect of time of day was also confirmed within both subgroups. With regard to instructions not to smoke, extraction was a moderator. Within unextracted samples, instructions not to smoke were associated with higher oxytocin measurements, whereas this effect was not replicated within extracted samples. In line with the results of the main analyses, none of the remaining fasting exerted significant effects in neither of the subgroups.

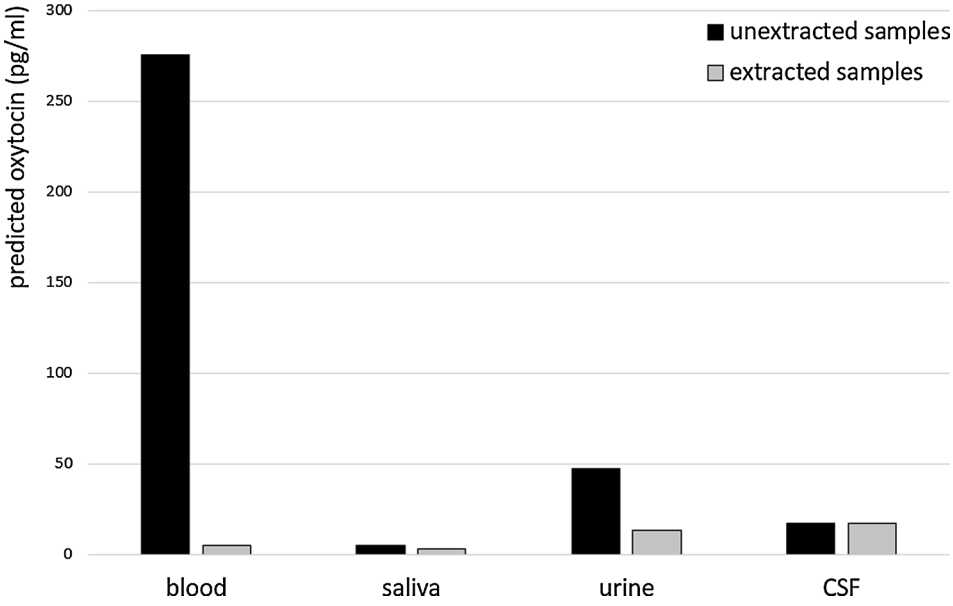

Fig. 2. Predicted endogenous oxytocin concentrations in extracted vs. unextracted blood, saliva, urine and cerebrospinal fluid (CSF) samples.

Table 3
Investigation of potential confounders.

Predictor	Number of subsamples[a]	β (*SEM*)	*t*	*p*	CI
Main analyses across unextracted and extracted samples					
Sex	330	0.00 (0.00)	7.28	< 0.01	0.00; 0.00
Age	243	0.03 (0.01)	2.00	< 0.05	0.00; 0.06
Time of day	219	0.08 (0.02)	4.04	< 0.01	0.04; 0.11
Eat	339	0.04 (0.06)	0.70	0.48	−0.08; 0.17
Drink	339	0.01 (0.07)	0.22	0.83	−0.12; 0.15
Caffeine	339	0.02 (0.07)	0.33	0.74	−0.11; 0.15
Smoking	339	0.09 (0.04)	2.28	0.02	0.01; 0.18
Alcohol	339	0.01 (0.07)	0.22	0.83	−0.12; 0.15
Exercise	339	0.02 (0.17)	0.13	0.90	−0.31; 0.35
Fast	339	0.03 (0.06)	0.43	0.66	−0.10; 0.16
Subgroup analyses within unextracted samples					
Sex	90	0.00 (0.00)	2.60	0.01	0.00; 0.00
Age	83	−0.01 (0.02)	−0.59	0.56	−0.05; 0.02
Time of day	71	0.10 (0.02)	4.88	< 0.01	0.06; 0.13
Eat	95	0.18 (0.29)	0.63	0.53	−0.40; 0.76
Drink	95	0.61 (0.37)	1.66	0.10	−0.12; 1.33
Caffeine	95	0.43 (0.31)	1.37	0.17	−0.19; 1.06
Smoking	95	0.23 (0.05)	4.33	< 0.01	0.12; 0.33
Alcohol	95	0.47 (0.31)	1.49	0.14	−0.15; 1.09
Exercise	95	0.60 (0.48)	−1.26	0.21	−1.56; 0.35
Fast	95	0.44 (0.28)	1.58	0.12	−0.11; 0.99
Subgroup analyses within extracted samples					
Sex	240	0.00 (0.00)	6.67	< 0.01	0.00; 0.00
Age	160	−0.04 (0.02)	−1.73	0.09	−0.09; 0.01
Time of day	148	0.23 (0.09)	2.50	0.01	0.05; 0.42
Eat	244	−0.08 (0.06)	−1.20	0.23	−0.20; 0.05
Drink	244	−0.07 (0.07)	−0.98	0.33	−0.21; 0.07
Caffeine	244	−0.11 (0.07)	−1.60	0.11	−0.24; 0.02
Smoking	244	−0.06 (0.07)	−0.89	0.37	−0.20; 0.08
Alcohol	244	−0.09 (0.07)	−1.22	0.22	−0.22; 0.05
Exercise	244	0.15 (0.18)	0.82	0.41	−0.21; 0.51
Fast	244	−0.10 (0.07)	−1.43	0.15	−0.23; 0.04

Note. Potential confounders were subsequently added to the baseline regression model. Study- and assay-related heterogeneity were considered as variance component. Additionally, the sample-level regressors year (reference: 2 000 years AD, scale: 10 years), risk of bias and appropriateness score (0–30 points), SEM of oxytocin value reported in the primary study in order to adjust for bias using the PET-PEESE method (Stanley and Doucouliagos, 2014), specimen (reference: blood) and extraction (reference: unextracted samples) were considered. The following sample-level regressors were tested: sex (percentage of women per sample), age (reference: 30 years, scale: 10 years), time of day (reference: 12 am/midnight, scale: 3 h), instructions not to eat, drink, consume caffeine, smoke, consume alcohol, exercise or any fasting instructions, considered as given (1) or not given/not reported (0). Missing values on fasting variables were imputed to 0. CI = confidence interval.

[a] Numbers vary as for some predictors, information was not reported in all primary studies.

3.3.4. Diurnal rhythm of endogenous oxytocin concentrations

The significant impact of time of day suggested a possible diurnal variability of endogenous oxytocin concentrations. To test for time-related fluctuations, we performed cosinor-based rhythmometry (Cornelissen, 2014). In this model, two linear predictors, reflecting different parameters of circadian change, jointly moderated the outcome (see supplementary material 5). Therefore, diurnal fluctuations of endogenous oxytocin can be assumed. Predicted oxytocin concentrations tended to decrease during the nighttime, reaching a nadir at 8 a.m., before steadily increasing during the day, with peak concentrations between 7 p.m. and 8 p.m. However, it is worth noting that the actual data basis for this prediction only covered a 16 h period from 6 a.m. to 10 p.m. The course of oxytocin concentrations during the remaining hours was estimated based on our model and has no actual data basis. Therefore, a valid conclusion can only be made with regard to the increase of endogenous oxytocin concentrations from morning to afternoon.

4. Discussion

4.1. Summary of evidence

This is the first systematic review and meta-analysis to address the impact of different kinds of specimen, extraction, participants' sex and age, as well as time of day of sampling, and fasting instructions in 326 studies assessing basal endogenous oxytocin. We applied meta-regressions to test whether sample-level differences in these variables explained variability in reported oxytocin concentrations. We were able to estimate the confounders' impact based on a large database of 229 primary studies comprising 339 subsamples and 12 741 participants, even though the studies were not explicitly designed to address this scientific question.

Previous research has discussed specimen (Hoffman et al., 2012; Valstad et al., 2017) and extraction (Szeto et al., 2011) as reasons for heterogeneity in oxytocin concentrations. Our results confirmed that oxytocin was differentially reflected in blood, saliva, urine, and CSF. This is in line with previous research challenging an assumed correlation between basal concentrations in different specimens (Hoffman et al., 2012; Valstad et al., 2017) and emphasizes that future research is required to understand the exact pathways and possible interindividual differences of oxytocin distribution through the human body. Moreover, we detected a specimen-specific impact of extraction. In line with Szeto et al. (2011), we showed that the difference between oxytocin concentrations derived from unextracted and extracted samples was high in blood samples. On the other hand, our results show a weaker impact of extraction in urine and, in line with previous research (Jong et al., 2015), no impact of extraction in saliva or CSF samples. Overall, this study confirms that attention to specimen and extraction is of utmost importance when interpreting and comparing results from clinical studies on endogenous oxytocin (Jong et al., 2015; Leng and Sabatier, 2016; McCullough et al., 2013; Szeto et al., 2011).

With regard to confounders, our results showed that oxytocin levels were higher in samples with higher percentages of female participants. This seems unsurprising, as oxytocin has often been associated with typically female life events and behaviors, such as giving birth (Macdonald and Macdonald, 2010), affectionate parenting styles (Feldman et al., 2007), or tend-and-befriend stress reactions (Taylor et al., 2000). Moreover, estrogens seem to promote oxytocin synthesis (Gabor et al., 2012; Lim and Young, 2006).

The meta-analysis also showed that oxytocin concentrations were higher in samples with a higher mean age, supporting the idea that oxytocin-related events, such as bond formations, parenting, or grandparenting, which accumulate throughout the lifespan, exert an impact on the oxytocin system (Huffmeijer et al., 2013). However, this effect was not replicated within the subgroups of studies using unextracted and extracted samples, respectively, and therefore, it can be assumed that the effect is relatively small, if existent.

While a diurnal rhythm of oxytocin release has already been discussed (Macdonald and Feifel, 2013), its course seems surprising. Our results indicated that concentrations were lower when oxytocin was measured in the morning higher when it was measured in the afternoon. Five of the included primary studies conducted within-subjects measurements of endogenous oxytocin concentrations over day- and night-cycles and detected either no significant fluctuations (Amico et al., 1983; Graugaard-Jensen et al., 2014) or different patterns than those detected by our study (Forsling et al., 1998; Kling et al., 1994; Landgraf et al., 1982). However, as these studies were based on small sample sizes, they do not permit a fair comparison with our results or

allow for speculation about factors that might have contributed to the diverging findings. To complement our study and to gain an understanding of the opposing results of previous preliminary research, we encourage the investigation of diurnal rhythms using large samples and longitudinal within-subjects designs. Such studies should also take possible moderators of diurnal variability into account. For instance, as cortisol, which is known to interact with oxytocin (Brown et al., 2016), displays a clear awakening response (Pruessner et al., 1997), it might be worthwhile to consider awakening time.

Lastly, our study showed that instructions to refrain from smoking led to higher oxytocin concentrations in unextracted blood samples. This extraction-specific effect is in line with evidence indicating that unextracted samples are more sensitive to influences of the sampling protocol (Robinson et al., 2014). Therefore, and in accordance with McCullough et al. (2013) who concluded that assays measuring oxytocin in extracted compared with unextracted blood are in general better validated, it can be argued that in blood samples, extraction should be the method of choice.

4.2. Limitations and future directions

It is worth noting that the fasting variables indicated whether or not authors reported that they instructed participants to refrain from certain behaviors before sampling. By this means, we created a proxy to estimate the impact of these behaviors on oxytocin concentrations. However, it was not possible to gather information concerning the actual compliance with these instructions. Therefore, the provision of instructions seemed to be the best estimation for the behavior of interest. Nevertheless, it needs to be noted that these variables only reflect assumed rather than actual behavior. This might explain discrepancies between our meta-analysis' results and findings from previous empirical studies that specifically investigated the impact of certain behaviors on oxytocin secretion. For instance, studies using within-subjects designs showed increased oxytocin measurements after physical exercise (Jong et al., 2015; Landgraf et al., 1982), whereas our meta-analysis did not detect between-studies differences depending on instructions to rest before the collection of baseline samples. These discrepancies emphasize that our results do not definitely prove that eating, drinking, caffeine consumption and exercise are irrelevant confounders of endogenous oxytocin measurements. Instead, we recommend conducting more studies with adequate designs that specifically address this question. Therefore, researchers that measure endogenous oxytocin concentrations to address scientific questions which are unrelated to these behaviors should at least record them to exclude any possible confounding impact on their data.

Moreover, we were unable to use a validated scale for the risk of bias rating. Due to the variety of included study designs, it was impossible to find a scale that suited the pool of heterogeneous studies. Our self-developed items ensured that studies with higher estimated study quality and precise fit to our study purposes were considered more strongly in our regression models. These items represent an approximation of these constructs but are not comparable with a validated scale.

It should be a matter of course that laboratories that offer to analyze endogenous oxytocin concentrations adequately validated their assays beforehand. However, it is worth noting that even though we used a variance component to control for assay-related heterogeneity, we were lacking insights into practices in each laboratory and were therefore unable to differentiate for quality standards.

Although we showed the impact of selected important confounders of endogenous oxytocin concentrations, this review should not be regarded as comprehensive. In fact, in another meta-analysis (Engel et al., 2019) we showed that oxytocin concentrations also fluctuate during the course of the menstrual cycle. In females, an impact of menopause, number of pregnancies and births, or hormonal contraception use might also be assumed. In this context, Bale and Epperson (2017) argue that female variability should not be used as an argument to exclude women from empirical studies. Instead, more research should be conducted to gain a deeper understanding of this variability. Other possible sex-unspecific confounders of endogenous oxytocin which were beyond the scope of this study are medication use, body mass index, habitual smoking, or relationship status. More studies and systematic overviews focusing on the impact of these possible confounders are warranted.

4.3. Conclusions

Endogenous oxytocin measurements can be a potent tool to assess possible dysregulations of the oxytocin system in mental disorders, as they are mostly non-invasive and allow repeated sampling over time and simultaneous measurements of different hormones from the same sample (Crockford et al., 2014). However, caution is required when interpreting and comparing results from clinical studies on endogenous oxytocin based on different specimens. Particularly in blood samples, the impact of extraction needs to be taken into account, as well. Moreover, we encourage researchers to consider the confounders identified in this meta-analysis in future studies in order to minimize methodological noise and strengthen trust in measurements of endogenous oxytocin in the context of mental disorders. Specifically, participants' sex, age and smoking behavior as well as the time of day of sampling should be reported. Ideally, their impact should be controlled for statistically or by the study design.

Acknowledgments

SE would like to express her gratitude to the "Stiftung der Deutschen Wirtschaft" for providing her doctoral funding. The foundation had no influence on the study design, the collection, analysis and interpretation of data, the writing of the report or the decision to submit the manuscript for publication.

All authors would like to thank Ludwig Ohse for his support in the grey literature search and his correspondence with authors of registered trials. We are grateful to Anya Deubel, Hannah Klusmann, and Annika Walinski, who assisted in gathering full-text articles. We also owe thanks to Hannah Klusmann and Annika Walinski for their help in the study selection process, data extraction and risk of bias and appropriateness rating. We are grateful to Sarah Mannion for proof-reading the manuscript. Finally, we deeply appreciate the generosity of all authors of the included studies who provided us with the full texts and the requested data for the present meta-analysis.

Contributors

SE and SSch designed the study. HN provided methodological advice. SE performed the literature search, coordinated the data collection, and contacted the authors of all primary studies for which relevant data were missing. SE, SL, HK and AW performed the study selection, data collection and inspection, as well as the risk of bias and appropriateness rating. RM performed the statistical analysis and drafted the report of the results. SE drafted the manuscript. SSch and CK supervised the meta-analysis. SL, RM, HN, CK and SSch revised the manuscript for important intellectual content.

Declaration of Competing Interest

Mrs. Engel, Mr. Laufer, Dr. Miller, Dr. Niemeyer, Prof. Dr. Knaevelsrud and Dr. Schumacher have no conflicts of interest to declare.

Financial disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yfrne.2019.100775.

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