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Did you drink alcohol during pregnancy? Inaccuracy and discontinuity of women's self-reports: On the way to establish meconium ethyl glucuronide (EtG) as a biomarker for alcohol consumption during pregnancy

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ABSTRACT

Consuming alcohol during pregnancy is one of the most verified prenatal risk factors for impaired child development. Information about the amount of alcohol consumed prenatally is needed to anticipate negative effects and to offer timely support. Women's self-reports are not reliable, often influenced by social stigmas and retrospective recall bias, causing biomarkers of intrauterine ethanol exposure to become more and more relevant. The present study compares both women's gestational and retrospective self-reports of prenatal alcohol consumption with levels of ethyl glucuronide (EtG) in meconium. Women (n = 180) gave self-reports of prenatal alcohol consumption both during their 3rd trimester (gestational self-report) and when their children were 6–8 years old (retrospective self-report). Child meconium was collected after birth and analyzed for EtG. No individual feedback of children's EtG level was given to the women. All analyses were run separately for two cut-offs: 10 ng/g (limit of detection) and 120 ng/g (established by Goecke et al., 2014). Mothers of children with EtG values above 10 ng/g (n = 42) tended to report prenatal alcohol consumption more frequently. There was no trend or significance for the EtG cut-off of 120 ng/g (n = 26) or for retrospective self-report. When focusing on women who retrospectively reported alcohol consumption during pregnancy, a claim to five or more consumed glasses per month made an EtG over the 10 ng/g and the 120 ng/g cut-off more probable. Women whose children were over the 10 ng/g EtG cut-off were the most inconsistent in their self-report behavior, whereas the consistency in the above 120 ng/g EtG group was higher than in any other group. The next step to establish EtG as a biomarker for intrauterine alcohol exposure is to correlate EtG values in meconium with child developmental impairments.

Introduction

Consuming alcohol during pregnancy is one of the most verified prenatal risk factors (Polańska, Jurewicz, & Hanke, 2015). However, prevalence of gestational alcohol consumption is still approximately 20% (Lanting, van Dommelen, van der Pal-de Bruin, Bennebroek Gravenhorst, & van Wouwe, 2015; Melchior et al., 2015; O'Keeffe et al., 2015). Epidemiological data are based on women's self-reports, which are prone to understatement (Todorow, Moore, & Koren, 2010), and many cases are likely to go unreported. The most severe consequence of prenatal alcohol consumption is Fetal Alcohol Syndrome (FAS), which is characterized by smaller size, lighter weight, and distinct facial abnormalities at birth (Landgraf, Nothacker, & Heinen, 2013). However, in cases of low to moderate alcohol consumption, developmental

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consequences are often not immediately obvious: Newborns seem to be unimpaired, there are no physical abnormalities, but effects on brain development are subtle and probable (Dörrie, Föcker, Freunscht, & Hebebrand, 2014). In particular, earlier findings suggest neurobehavioral and cognitive impairments comparable to symptoms of Attention Deficit Hyperactivity Disorder (ADHD) (Burger et al., 2011). Information about the consumed amount of alcohol during pregnancy is needed to anticipate negative effects on child development. There are three current options for the assessment of prenatal alcohol consumption:

A. Measure child developmental impairments.
B. Ask the woman.
C. Analyze biomarkers of the woman or child.

Options to measure child developmental impairment are restricted and this method often results in a very late diagnosis. In one study, 100% of children diagnosed in childhood with FAS had no detectable symptoms at birth (Little, Snell, Rosenfeld, Gilstrap, & Gant, 1990). Therefore, it seems essential to ask the woman about gestational alcohol consumption, which is the most direct and cheapest assessment method, but simultaneously the least reliable.

When asking women about alcohol consumption during pregnancy, the majority deny consumption (Derauf, Katz, & Easa, 2003: 95%; Goecke et al., 2014: 79%). In populations with heavy drinking (risk sample populations), where gestational alcohol consumption is not generally socially discouraged, percentages of denying self-reports are lower (Himes et al., 2015: 31%). However, even in these populations systematic underreporting is an issue. In their review concerning the influence of low to moderate alcohol consumption during pregnancy on child development, Todorow et al. (2010) drew the conclusion that the underreporting in women's self-reports is influenced by retrospective recall bias and social stigmas regarding alcohol use during pregnancy.

If self-reports at one assessment time are of low reliability, perhaps repeating the surveys at different assessment points could help. Currently, it remains unclear if there are specific patterns of self-reporting, for example, denying alcohol consumption when asked during pregnancy and reporting in retrospect. Gollenberg and colleagues (Gollenberg, Mumford, Cooney, Sundaram, & Louis, 2011) have already demonstrated that self-report of alcohol consumption shows the most lack of reliability in comparison with other behavioral self-reports (caffeine, nicotine), both asked during pregnancy and 10 years later.

The last option, establishing child biomarkers which represent alcohol consumption during pregnancy, focuses on metabolites of ethanol. Ethyl glucuronide (EtG) is a minor ethanol metabolite and can be detected in the first stool (meconium) of the newborn, passed within 72 h after birth. EtG has been established in several studies as a biomarker of fetal ethanol exposure during the third trimester of pregnancy (see for review Burd & Hofer, 2008; Joya et al., 2016). Meconium accumulates in the fetal gut from around the 20th week of gestation until birth. The majority of the meconium (75%) is created during the last 8 weeks of pregnancy. Positive cut-off (limit of detection) for intrauterine alcohol exposure varies slightly from study to study, but a minimum of 10 ng/g EtG argues for fetal alcohol exposure during the 3rd trimester (Bakdash et al., 2010; Himes et al., 2015).

In order to establish EtG as a biomarker for low to moderate gestational alcohol consumption, for use in clinical practice, earlier studies focused on correlation with women's self-reports. However, it has been demonstrated in several studies that women's self-reports during pregnancy, due to the above-named biases, do not satisfactorily correlate with meconium biomarkers. Specifically, in general population samples and at times when EtG was high, the correlation was small (Goecke et al., 2014). Correlations were higher in heavy alcohol-consuming populations, indicated by fewer social stigmas and a wider range of reported drinking levels (Himes et al., 2015). Nonetheless, in a review by Lange et al (Lange, Shield, Koren, Rehm, & Popova, 2014) comparing the amount of ethanol metabolites in meconium with women's self-reports during pregnancy, a four-fold understatement of alcohol consumption by self-report was found. Correlation of retrospective women's self-report (for example, when the child has reached school age) with meconium biomarkers has been missing until now.

The present study includes, for the first time, both gestational women's self-reports and retrospective women's self-reports simultaneously. Additionally, two EtG thresholds were compared for significance (10 ng/g and 120 ng/g). The hypotheses were:

1. *Inaccuracy: Between-subject effects.* Mothers of EtG-positive children and mothers of EtG-negative children do not differ in their gestational (3rd trimester) and retrospective (child 6–8 years old) self-report of alcohol consumption during pregnancy. The hypothesis applies to both groups separated by 10 ng/g and 120 ng/g EtG thresholds.
2. *Discontinuity: Within-subject effects.* There is no significant correlation between gestational and retrospective women's self-reports of alcohol consumption during pregnancy for mothers of EtG-positive children. Mothers of EtG-negative children are more consistent. This hypothesis applies to both the groups separated by 10 ng/g and 120 ng/g EtG thresholds.

Materials and methods

Study design

The present study included two assessment times: 2005–2007 (first assessment) and 2012–2015 (second assessment). In the first assessment, pregnant women, recruited as outpatients at the department of obstetrics and gynecology during their 3rd trimester without preselection, took part in FRAMES (**Fra**nconian **M**aternal Health **E**valuation **S**tudies, Goecke et al., 2014; Reulbach et al., 2009). Child meconium was collected after birth (Bakdash et al., 2010). The second assessment took place when the children were 6–8 years old. Both women and children were re-assessed in the follow-up study FRANCES (**Fran**conian **C**ognition and **E**motion **S**tudies). At both time points, women completed a self-rating question concerning their alcohol consumption during pregnancy (question seen in Fig. 1). Women never received individual feedback of their child's meconium EtG levels.

The study was approved by the Local Ethics Committee and was conducted in accordance with the Declaration of Helsinki. All patients gave informed consent.

Participants

The present paper reports the results of $n = 180$ women with complete data sets, who took part in both FRAMES and FRANCES data collection. At the time of childbirth, participants were an average of 32.8 ($SD = 4.67$) years of age, ranging from 19 to 44. Of the 180 participants, 42 (23%) children were EtG-positive with ≥10 ng/g and 26 (14%) with ≥120 ng/g in meconium. Women with EtG-negative vs. EtG-positive children, based on both the 10 ng/g and 120 ng/g thresholds, did not differ during their third trimester in age [10 ng/g: $t(178) = -.37$, $p = .711$; 120 ng/g: $t(178) = -.02$, $p = .982$], secondary education level [10 ng/g: $\chi^2(1, N = 179) = .00$, $p = .962$; 120 ng/g: $\chi^2(1, N = 179) = .00$, $p = .963$], marital status [10 ng/g: $\chi^2(1, N = 179) = .25$, $p = .620$; 120 ng/g: $\chi^2(1,$

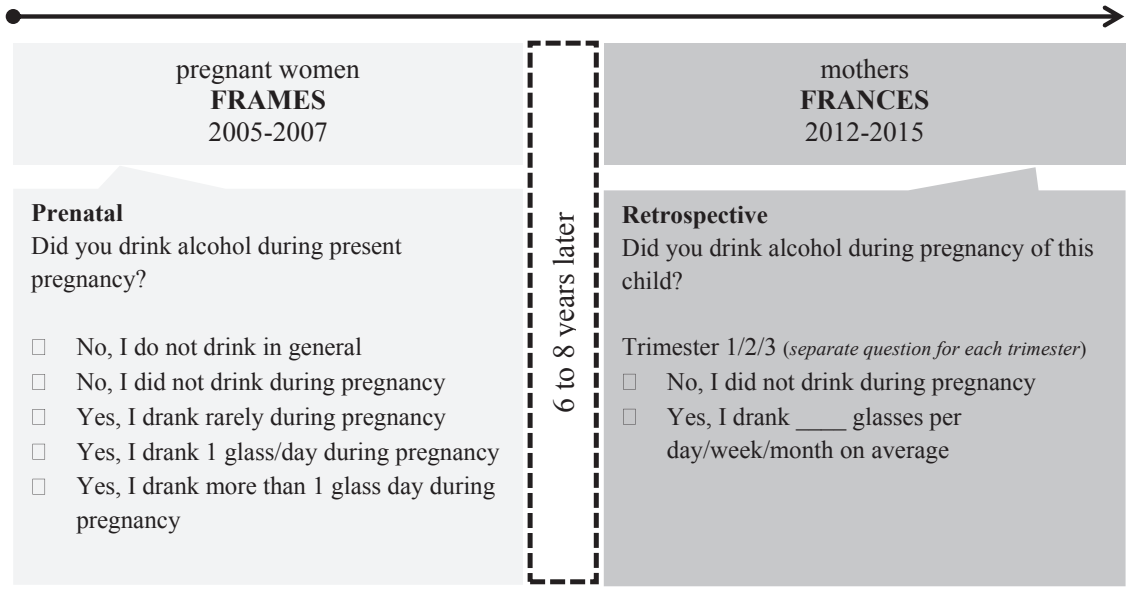

Fig. 1. Questions of women's gestational (FRAMES) and retrospective (FRANCES) self-reports.

$N = 179) = .54$, $p = .464$] or scores on the subscale Openness of the Freiburg Personality Inventory [FPI, Fahrenberg, Hampel, & Selg, 2010; 10 ng/g: $t(171) = -1.12$, $p = .264$; 120 ng/g: $t(178) = -.54$, $p = .593$].

Measures

EtG

The first positive cut-off of EtG ≥10 ng/g (limit of detection) was applied in reference to laboratory studies (Bakdash et al., 2010). The second positive cut-off of EtG ≥120 ng/g was established by Goecke et al. (2014) in a study based on a comparable sample: Above this value, women's self-report behavior inverted, i.e., drinking alcohol during pregnancy was underreported more frequently. In the following text, women who have given birth to children with EtG values above vs. below the cut-offs will be called EtG-positive vs. EtG-negative. One gram of meconium was collected from the newborns within the first 2–24 h after birth and frozen at −80 °C for up to 30 months before analysis. The procedure for the determination of EtG has been described in detail by Bakdash et al. (2010).

Gestational and retrospective self-report of alcohol consumption

Gestational self-report: In the context of FRAMES, women were asked in a structured interview (face-to-face format) about their drinking behavior during pregnancy (questions seen in Fig. 1). For data analysis, two groups were created based on women's self-reports: no drinking ("I don't drink in general" + "I didn't drink during pregnancy") vs. drinking ("I rarely drank during pregnancy" + "I drank one glass/day during pregnancy"). No woman reported more than one glass/day. Women were not asked during their pregnancy about the concrete amount of consumed drinks.

Retrospective self-report: In the context of FRANCES, women answered standardized questions (paper-and-pencil format) about drinking behavior during their pregnancy with the participating child (question seen in Fig. 1). Drinking behavior during pregnancy was retrospectively asked separately for each trimester. For further analyses, the reported number of drinks for trimester 2 and 3 were combined into one index. Analyses are based on number of glasses/month.

Statistics

The analyses were carried out using the statistical software IBM SPSS Statistics (Version 21.0, Armonk, NY: IBM Corp., 2012). To test inaccuracy of women's self-reports, EtG-positive vs. EtG-negative cases were compared for their gestational self-reports and retrospective self-reports. For gestational self-reports, chi-square (χ^2) tests (effect size: phi coefficient, Φ) were used to compare drinking behavior ("I did not drink during pregnancy" vs. "I drank during pregnancy"). Retrospective self-reports were not distributed normally and as such, non-parametric *U* tests (effect size: Cohen's *d*) were used to compare mean consumption scores (consumed glasses/month during pregnancy). Since, in a general population, it is rare to confess alcohol consumption in pregnancy, a *U* test was added that compared only EtG-positive vs. EtG-negative women, who retrospectively reported drinking a minimum of one glass/month.

To test the discontinuity of EtG-positive women's self-reports, gestational and retrospective answers were dichotomized (no drinking vs. any drinking) and the repeated measures were tested for consistency in χ^2 tests. Analyses were first run for the total sample and then separated for the EtG-positive and EtG-negative cases. All analyses were run separately for EtG threshold ≥10 ng/g and EtG threshold ≥120 ng/g. No confounders were included because in our own pre-analyses, as well as in the study of Goecke et al. (2014), EtG-positive vs. EtG-negative cases did not differ in sociodemographic variables.

Results

Descriptive: EtG

The mean EtG value of EtG-positive cases was 588 ($SD = 1604$) and ranged from 17 ng/g to 10,235 ng/g. After log-transformation $lg_{10}(x + 1)$ of EtG measures ($M = .53$, $SD = 1.00$), even the highest value of 10,235 ng/g ($EtG_{lg10} = 4.01$) remained within 3.5 *SD* (for

Table 1
Inaccuracy of self-reports: Gestational and retrospective self-reports of alcohol consumption during pregnancy for total group and compared for EtG-positive vs. EtG-negative cases.

EtG thresholds:	Total	<10 ng/g	≥10 ng/g	<120 ng/g	≥120 ng/g
n	180	138	42	154	26
Gestational					
No alcohol					
n (%)	137 (76)	109 (79)	28 (67)	119 (77)	18 (69)
Yes, rarely					
n (%)	42 (23)	29 (21)	13 (31)	35 (23)	7 (27)
Yes, one glass/day					
n (%)	1 (1)	–	1 (2)	–	1 (4)
[a]χ^2(df = 1) (Φ)		2.69 (.122), $p = .100^{+}$		.79 (.066), $p = .374$	
Retrospective					
No alcohol					
n (%)	161 (89)	124 (90)	37 (88)	138 (90)	23 (89)
Yes, x glasses/month					
n (%)	19 (11)	14 (10)	5 (12)	16 (10)	3 (11)
M (*SD*)	.23 (.95)	.14 (.56)	.55 (1.66)	.16 (.64)	.65 (1.94)
U test all cases, *z* (*d*)		−.51 (.44), $p = .607$		−.35 (.52), $p = .728$	
Retrospectively reported glasses/month	***n***	***n***	***n***	***n***	***n***
Glasses/month					
1	10	10	–	10	–
2	3	2	1	3	–
4	4	2	2	3	1
5	1	–	1	–	1
8	1	–	1	–	1
U test drinking cases, *z* (*d*)		−2.83 (2.13), $p = .003^{**}$		−2.57 (2.86), $p = .004^{**}$	

Gestational: self-report at 3rd trimester; retrospective: self-report when child was 6–8 years old. Chi-square tests (test statistic χ^2, df = degrees of freedom): effect size phi coefficient Φ; *U* test (test statistic *z*): effect size Cohen's *d*.
$^{+}p < .10$, $^{**}p < .01$.
[a] Dichotomous: no drinking vs. drinking.

outlier analysis also see Bakdash et al., 2010). Forty-two children had an EtG ≥10 ng/g and 26 children had an EtG ≥120 ng/g. For the following analyses the total sample was split along the two EtG cut-offs in EtG-positive vs. EtG-negative groups (Table 1).

Descriptive: gestational and retrospective self-report of alcohol consumption

From the total sample, 24% reported alcohol consumption in the gestational self-report, yet retrospectively only 11% of women reported consumption. This pattern was also found in the EtG-positive groups (≥10 ng/g/≥120 ng/g): 14 out of 42 (≥10 ng/g) and 8 out of 26 (≥120 ng/g) women reported during gestation; 5 out of 42 (≥10 ng/g) and 3 out of 26 (≥120 ng/g) women reported retrospectively. The variance of retrospectively reported glasses/month was uniformly higher in EtG-positive than EtG-negative groups (Levené Test: 10 ng/g $F = 27.1$, $p = .000$, 120 ng/g $F = 27.4$, $p = .000$).

Inaccuracy: self-reports of EtG-positive vs. EtG-negative cases

In gestational self-report, EtG ≥10 ng/g positive women tended ($p < .10$) to report more often to "drink rarely" than EtG-negative women, with a small effect size (Table 1). When a woman reported alcohol consumption during pregnancy in the gestational self-report, the risk for a child with a meconium EtG ≥10 ng/g was 1.8 times greater than when no alcohol consumption was reported (Odds Ratio, 95% CI [.88, 4.02]). A relevant prediction was not found for the 120 ng/g cut-off. Groups, regardless of the cut-off, did not differ in retrospectively reported amount of consumed glasses/month (range: 0–8). When only women with a retrospectively reported minimum of one glass/month were included ($n = 19$), amounts of reported glasses/month were consistently higher in the EtG-positive groups (EtG ≥10 ng/g [$n = 5$]: $M = 4.60$, $SD = 2.19$; EtG ≥120 ng/g [$n = 3$]: $M = 5.67$, $SD = 2.08$) than EtG-negative groups (EtG <10 ng/g [$n = 14$]: $M = 1.38$, $SD = 1.23$; EtG <120 ng/g [$n = 16$]: $M = 1.58$, $SD = 1.32$). The effect size was high for both groups (Table 1 and Fig. 2).

Inconsistency: comparison of gestational and retrospective self-report

Despite the EtG values, in 95% of cases in which women denied alcohol consumption in the gestational self-report, the women also denied alcohol consumption in the retrospective self-report. However, only 28% of the women who reported alcohol consumption in the gestational self-report also reported it in the retrospective self-report (Table 2).

There was a significant correlation of gestational and retrospective women's self-reports in the EtG <10 ng/g negative group. This correlation could not be found in the EtG ≥10 ng/g positive group, due to the increasing frequency of women who denied

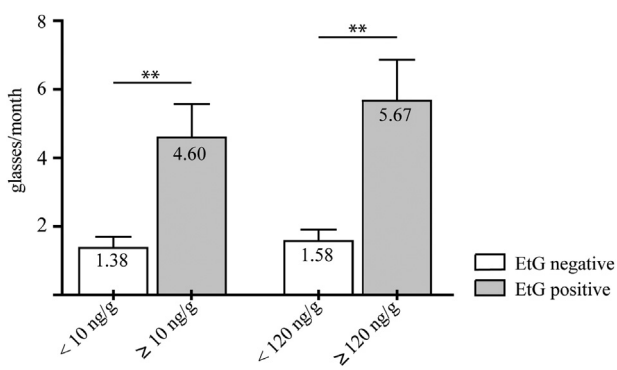

Fig. 2. Retrospectively reported glasses per month in EtG-negative vs. EtG-positive groups along two EtG cut-offs. $^{**}p \leq .01$.

Table 2
(Dis)continuity of self-reports: gestational vs. retrospective self-reports of alcohol consumption during pregnancy for total group and in separate for EtG-positive and EtG-negative cases.

EtG thresholds	Total		<10 ng/g		≥10 ng/		<120 ng/g		≥120 ng/g	
n	180		138		42		154		26	
χ^2(df = 1) (Φ)	18.02 (.316)		17.58 (.357)		1.82 (.208)		11.43 (.272)		7.63 (.542)	
p	.000**		.000**		.178		.001**		.006**	
	Retrospective *n* (% of gestational category)									
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Gestational										
No	130 (94.9)	7 (5.1)	104 (95.4)	5 (4.6)	26 (92.9)	2 (7.1)	112 (94.1)	7 (5.9)	18 (100)	0 (0)
yes	31 (72.1)	12 (27.9)	20 (69.0)	9 (31.0)	11 (78.6)	3 (21.4)	26 (74.3)	9 (25.7)	5 (62.5)	3 (37.5)

Gestational: self-report at 3rd trimester; retrospective: self-report when child was 6–8 years old. Chi-square tests (χ^2, df = degrees of freedom): effect size phi coefficient Φ.
**$p < .01$.

alcohol consumption in the gestational self-report and reported it in the retrospective self-report or vice versa (Fig. 3).

In the EtG ≥120 ng/g positive group, the correlation of gestational and retrospective self-report, expressed by effect size, was higher than in any other group (see Table 2). This was primarily because all women who denied alcohol consumption in the gestational self-report also denied alcohol consumption in the retrospective self-report, and because more than one-third of women who admitted alcohol consumption in the gestational self-report also admitted alcohol consumption retrospectively.

Discussion

The present study aims to support the establishment of EtG, obtained from newborn meconium, as a biomarker for low to moderate levels of alcohol consumption during the last trimester of pregnancy. The potential practical use is to identify affected children early, resulting in timely developmental support.

We found that women with EtG-positive children did not differ significantly in their gestational or retrospective self-reports from women with EtG-negative children: In both groups, approximately 3 out of 10 women reported drinking alcohol during gestation and only 1 out of 10 women reported this retrospectively. This rate is similar to the prevalence found in other European studies (Lanting et al., 2015; Melchior et al., 2015; O'Keeffe et al., 2015). In correspondence with Goecke et al. (2014), who examined differences in patient characteristics, the absence of disparity in the self-reports of alcohol consumption between women with EtG-positive and EtG-negative children was most clear when the 120 ng/g cut-off was applied. The present study adds that not only the gestational self-report, but also the retrospective self-report, cannot differentiate between EtG-positive and EtG-negative cases, i.e., EtG-positive women deny alcohol consumption as often as EtG-negative women do. When focusing on the few women who reported alcohol consumption during pregnancy retrospectively, there is a significant difference in reported glasses/month between EtG-positive and EtG-negative cases: When a woman retrospectively reports five or more glasses per month, an EtG over the cut-off becomes more probable.

Since the sample of EtG-positive cases is small in the present study, the results need to be interpreted carefully. However, the results may accurately depict the true prevalence of alcohol consumption during pregnancy in the general population. The issue of low sample size was addressed by using non-parametric statistical tests, but external validity was still compromised by low sample size (some statistical combinations resulted in fewer than 10 cases). Due to this, the analysis should be replicated in a larger group. Additionally, we recommend asking for concrete amounts of consumed alcohol, even prenatally, since this revealed significant differences in the retrospective self-reports. The answer format should be structured to allow reporting alcohol consumption in glasses per day, week, month, or trimester. For instance, a validated approach that obtains detailed actual and retrospective estimates of daily drinking is the Timeline Followback (TLFB, Robinson, Sobell, Sobell, & Leo, 2014; Sobell & Sobell, 1995) which can be administered in a paper-and-pencil or interviewer format.

The present results, based on the total sample, do allow a further conclusion to be made for the general population: Self-reports are more biased when information about alcohol consumption during pregnancy is asked retrospectively. In our sample, fewer than half of the women who reported alcohol consumption in the gestational self-report reported retrospectively. This bias is most likely caused by a combination of social and recall bias. This is in accordance with Gollenberg et al. (2011), who also found that reports of alcohol consumption at different assessment points are not consistent.

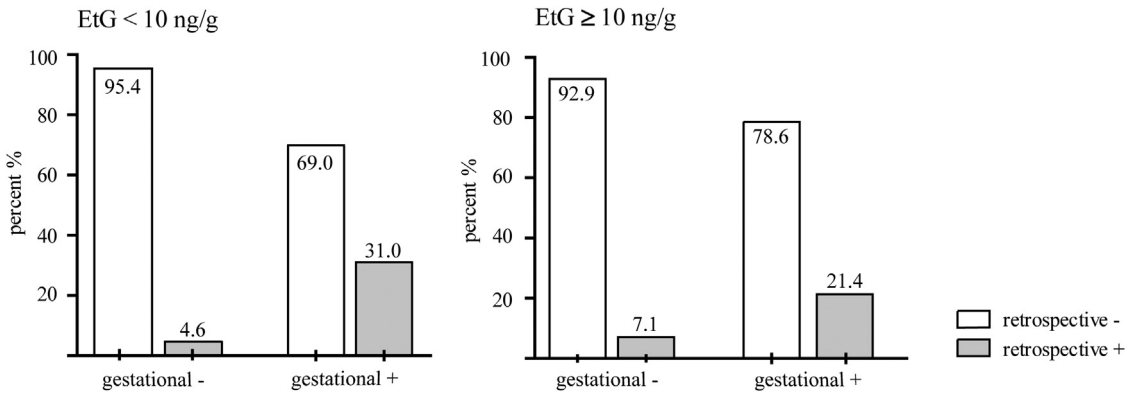

Fig. 3. Gestational and retrospective self-reports in combination: (Dis)continuity of self-reports in EtG 10 ng/g negative vs. positive cases ("+" alcohol consumption reported, "–" no alcohol consumption reported).

Nonetheless, the correlation of gestational and retrospective self-reports for the total sample is significant, primarily due to cases of consistent negation.

However, the picture changes when exclusively focusing on the EtG-positive group. Women with children over the EtG ≥10 ng/g cut-off are more inconsistent in their self-reported behavior and the 'gestational to retrospective' correlation did not reach significance: The percentage of women, who deny drinking in the gestational self-report and admit drinking in the retrospective self-report, and vice versa, is higher than in the EtG-negative group. The self-reports of women with children over the EtG ≥120 ng/g cut-off are more consistent: The percentage of women who admitted or denied in both the gestational and retrospective self-report is higher than in any other group. One explanation to be considered is that insecurity and repression in women with low levels of alcohol consumption leads to inconsistent reactions in self-report, while women who consume moderate amounts of alcohol are less inhibited and have a congruent strategy for self-report. However, the data on discontinuity of self-report still needs to be interpreted cautiously given the small number of EtG-positive cases and needs to be replicated in a larger sample.

For previous and future research, it must be considered that not only women's self-reports but also the biomarker EtG is not completely reliable. Some studies have assumed (Bakdash et al., 2010) or confirmed (Chan et al., 2003) that a heightened EtG reflects intrauterine alcohol exposure of the fetus, but the cause is not necessarily due to the mother drinking during pregnancy. Alternative explanations, i.e., ethanol traces contained in common foods (i.e., olive oil, fruit juice) or medicines, must be controlled for future research.

Regardless of the origin, it is clear that an EtG-positive child was exposed to intrauterine alcohol levels and is at risk for developmental abnormalities. Many authors criticize women's self-reports as a standard for establishment of ethanol metabolites in meconium (Derauf et al., 2003; Lange et al., 2014) and correlations to child development may be preferable. Until now there are only a few studies correlating ethanol metabolites in meconium with child developmental impairments. Peterson et al. (2008) as well as Min et al (Min, Singer, Minnes, Wu, & Bearer, 2015) tested for an alternative ethanol metabolite in meconium (fatty acid ethyl esters, FAEE) and found influences on child cognitive development in infancy, childhood, and adolescence. Studies concerning EtG are still pending.

What do these results mean for clinical practice? With the aim to detect low to moderate alcohol consumption during pregnancy in general non-risk populations, clinicians must realize that women's self-reports of alcohol consumption are not reliable. Neither gestational nor retrospective self-report measures correspond systematically with fetal intrauterine ethanol exposure markers in the 3rd trimester. Even though there is still a long way to go before we can establish EtG as a common biomarker in obstetric practice, we can suggest that the more promising research for further studies is the correlation of EtG meconium values with child development rather than focusing on correlating with women's self-reports.

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