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Moving beyond the mean: Promising research pathways to support a precision medicine approach to hormonal contraception

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ABSTRACT

Women's psychological and behavioral responses to hormonal contraceptive (HC) treatment can be highly variable. One of the great challenges to researchers seeking to improve the experiences of women who use HCs is to identify the sources of this variability to minimize unpleasant psychobehavioral side-effects. In the following, we provide recommendations for programs of research aimed at identifying sources of heterogeneity in women's experiences with HC. First, we review research demonstrating person- and prescription- based heterogeneity in women's psychobehavioral responses to HCs. Next, we identify several promising person- and prescription- based sources of this heterogeneity that warrant future research. We close with a discussion of research approaches that are particularly well-suited to address the research questions raised in article. Together, this review provides researchers with several promising research pathways to help support the development of a precision medicine approach to HC treatment.

1. Introduction

Hormonal contraceptives (HCs) have been life-changing for generations of women. Giving women the ability to better control the timing of pregnancy and childbirth has allowed them to set long-term educational and career goals, making them an important tool in women's upward social and economic mobility (Bailey, 2006; Goldin and Katz, 2002). HCs also offer non-contraceptive benefits to women, including reduced risk of ovarian cancer (Hannaford et al., 2007; Maia and Casoy, 2008; Tworoger et al., 2007; Vessey and Painter, 2006), reductions in heavy or painful menstrual bleeding (Stewart and Black, 2015), and improvements in premenstrual symptoms (e.g., PMS; e.g., Bertone-Johnson et al., 2014; Ito et al., 2021; Koci and Strickland, 2007) and the appearance of acne (Arowojolu et al., 2012).

Box 1. Abbreviations of Key Terms.

HC = hormonal contraceptive; any contraception containing hormones, including oral contraceptive pills, hormonal IUDs, implants, patches, rings, and injectables

OC = oral contraceptives (i.e., "the pill")
NC = naturally cycling (i.e., not taking any HCs)

Despite the benefits of HC use, some women are reluctant to use HCs or discontinue use because of concerns with unwanted side-effects (Hatcher et al., 2004; Ott et al., 2008). Nearly half of all women who go on HCs stop using them within the first year because of intolerable side-effects, particularly those affecting mood or sexual function (Sanders et al., 2001). Further, side effect concerns represent a frequently-cited reason that women resist beginning HC use in the first place (Le Guen et al., 2021), a trend that has been exacerbated in recent years by social media testimonials from women publicizing their negative experiences with HCs (Kissling, 2016; Le Guen et al., 2021; Vondráčková, 2020) and their decision to stop using them (Kissling, 2014). There has been a 9% decline in use of HCs in the US in the last fifteen years (Women's Health Policy, 2019), suggesting that women may be increasingly wary of hormonal forms of contraception because of its possible side-effects.

Although women are frequently concerned with HC side effects (Le Guen et al., 2021), researchers often fail to find differences between HC-treated and HC-untreated (i.e., naturally cycling [NC]) women when it comes to specific outcomes believed to be linked to HC use (e.g., weight gain, depression). The lack of mean differences between users and non-users has led many researchers and clinicians to conclude that HCs have relatively few side-effects, despite individual women's reports of having experiencing them. However, given the tremendous amount of heterogeneity in women's responses to HC treatment, such conclusions may be

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premature. While it may be true that many women may not experience some of the side-effects believed to be linked to HC treatment, others do. Understanding the sources of variability in women's responses to HC treatment therefore represents an important research opportunity for those hoping to conduct research that can translate from the laboratory to the clinic.

In the following, we provide recommendations for programs of research that promise to offer essential insight into the factors that impact women's experiences with HC side-effects, with a specific focus on those that are psychobehavioral in nature. In particular, we focus on research questions addressing woman- and prescription- specific factors that may impact women's positive or negative experiences with different HC regimens. With this goal in mind, we first review research demonstrating person- and prescription- based heterogeneity in women's psychobehavioral responses to HCs. Next, we identify several promising person- and prescription- based sources of this heterogeneity that warrant future research. We close with a discussion of research approaches that are particularly well-suited to such questions and identify ways that researchers can make their results maximally impactful on clinical practice.

2. The effects of HC treatment on neurobiological and psychobehavioral outcomes

Hormonal birth control is the most popular type of contraception used in industrialized countries (Daniels et al., 2015), with 82% of reproductive-aged women reporting having been on it at some point in their lives (Daniels and Jones, 2013). Since its FDA approval in 1960 (Bullough, 2001; Harris, 2002), the types and modalities of hormonal birth control have increased from a single type – a combination hormonal birth control pill containing 0.15 mg of mestranol (which converts to ethinyl estradiol by the liver) and 10 mg of norethynodrel (a first generation progestin) – to a product category containing more than 100 different formulations that are delivered via pill, shot, patch, subcutaneous implant, vaginal ring, and intrauterine device.

Because many commercially available HCs contain estrogens, they increase women's risks of experiencing certain types of dangerous thrombotic and cardiovascular events, including hypertension, blood clots, and strokes (Sherif, 1999). Accordingly, much of the early research on the impact of HCs on women was aimed at understanding the safety and efficacy of the drugs to ensure that the health risks to users were low and that the pregnancy protection benefits were high. It is only very recently that researchers have begun to explore the behavioral and neurophysiological effects of HCs (for a discussion, see Pletzer and Kerschbaum, 2014; Montoya and Bos, 2017), despite several-decades-long awareness that the human nervous system is an important target for the actions of sex hormones (e.g., McEwen and Alves, 1999). Because HCs introduce exogenous hormones of varying composition and doses and (as a result) suppress endogenous sex hormone production, the hormonal milieu they create within the bodies of users is likely to be quite different than what is present in the absence of treatment. Accordingly, the hormonal changes initiated by HC use are likely to impact neurobiological processes throughout the brain, including those involved in emotional and cognitive regulation (Almey et al., 2015; Brinton et al., 2008; Österlund et al., 2000; Rossetti et al., 2016; Wharton et al., 2012), those involved in learning and memory (Taxier et al., 2020; Frick, 2019; Frick et al., 2018; Galea et al., 2017; Hara et al., 2015), and many others.

Although comparably little is known about the impact of HCs on neurophysiology and women's psychobehavioral outcomes, emerging research finds that HC use is associated with a range of such effects. For example, structurally, researchers find HC use is associated with region-specific differences in grey matter volume. Specifically, this research finds that women using HCs exhibit higher grey matter volumes in the prefrontal cortices, pre- and postcentral gyri, hippocampus, parahippocampal and fusiform gyri, anterior cingulate cortex, and temporal regions[2] compared to NC women (Pletzer et al., 2010; 2015), but lower volumes in the left amygdala/anterior parahippocampal gyrus (Lisofsky et al., 2016). Others find that HC users exhibit less white matter integrity (De Bondt et al., 2013), and lower hippocampal volumes (Pletzer et al., 2019) than what is observed in NC women. Functionally, HC users have been found to exhibit differences in resting functional connectivity in executive control and default mode networks compared to NC women, differences that are moderated by the androgenicity of the HC a woman is using, and the age at which she began use (Petersen et al., 2014; Pletzer et al., 2016; Sharma et al., 2020).

While much of the research investigating structural and functional differences between the brains of HC and NC women is cross-sectional (thereby preventing a clear understanding of causality), one prospective, longitudinal study found that resting-state functional connectivity between the left amygdala/anterior parahippocampal gyrus and the dorsolateral prefrontal cortex changed from positive to negative in women after beginning HC treatment. The opposite was found to be true for women in the NC control group (Lisofsky et al., 2016). This is a region of the brain known to play a role in emotion regulation, suggesting that these differences may play a role in some of the mood-related changes that can occur among women taking HCs. Indeed, research finds emotional processing differences between HC users non-users, with HC users exhibiting decreased memory of negative emotional stimuli (Person and Oinonen, 2020), decreased amygdala activation in response to viewing negative emotional stimuli (Petersen and Cahill, 2015), heightened insula and dorsal anterior cingulate cortex activity while viewing a traumatic film (Miedl et al., 2018), and – in women with previous negative experiences with HCs – lower reactivity in the left insula, left middle frontal gyrus, and bilateral inferior frontal gyri in response to emotional stimuli, when compared to NC women or those given an HC placebo (Gingnell et al., 2013).

Research also finds that HC users exhibit differential brain activation in response to rewards compared to NC women. For example, HC users exhibit decreased anterior insula activation upon erotic stimulation and enhanced activation during monetary reward expectation (Abler et al., 2013; Bonenberger et al., 2013). Additionally, beyond these differences, research finds that HC use is associated with diminished libido (Boozalis et al., 2016; Casey et al., 2017; Smith et al., 2014), decreased perseverance on cognitive tasks (Bradshaw et al., 2020), and blunting of the HPA axis-mediated stress response (Kirschbaum et al., 1999; Kumsta et al., 2007; Lovallo et al., 2019; Merz, 2017; Nielsen et al., 2013; Rohleder et al., 2003; Roche et al., 2013).

Despite the growing body of work demonstrating important psychobehavioral and neurophysiological differences between HC users and non-users, it is also clear that many of these effects are idiosyncratic and can vary considerably between both women and HC products. Not all women respond the same way to the same HC regimen, and the way women feel on one product can be very different from the way that they feel on another. For example, in one study investigating the relationship between HC use and the risk of subsequent depression, the researchers

[2] Notably, Pletzer and colleagues (2015) also report differences in region-specific grey matter volumes between users of androgenic and anti-androgenic OCs. Compared to NC women, users of androgenic OCs possess smaller bilateral middle and superior frontal gyri, while users of anti-androgenic OCs possess larger bilateral fusiform gyri, fusiform face area, parahippocampal place area, and cerebellum volumes.

found that that the risk varied fairly dramatically depending on the women's age and type of HC they had been prescribed (Skovlund et al., 2016). For example, they found that the depression risk for the HC-taking adolescent women in their sample was, in some cases, more than double what it was for the adults. Additionally, they found that these risks varied considerably across product types and delivery modalities. The depression risk for those women prescribed non-oral HCs (e.g., the transdermal patch or vaginal ring), for example, was found to be significantly higher than what it was for women prescribed combined oral HC pills (Skovlund et al., 2016).

Unfortunately, studies investigating the relative impact of woman- or prescription-specific effects of HC on women's side effect profile are the exception rather than the rule. This is particularly true of research measuring psychological and behavioral outcomes associated with HC use, which often group all types of women on all types of products together. This means that an effect of HC use on any reported outcome will only make itself known to researchers if it occurs in *all* types of users, on *all* types of products currently in use. However, given the heterogeneity of women's responses to sex steroid hormones and the range of HC products available to women (there are over 100 different formulations available as of this writing), it is unlikely that this occurs very often. Indeed, this approach towards researching the impact of HC use on women's psychologies and behaviors is likely at the heart of the number of inconsistencies and seemingly contradictory results in this literature, as well as the disconnect that sometimes exists between women's reported experiences on HCs and the results of research studies.

Take for example the issue of HC use and weight gain. Although weight gain falls outside the purview of neuropsychological effects, it is an issue that many women considering using HCs are concerned with. Women routinely report experiencing weight changes in response to HC use, and undesired changes in body weight are one of the top three reasons that women discontinue HC use (see e.g., Al-Ghashri et al., 2021). A review of the extant research literature examining links between HC use and weight gain, however, would lead one to conclude that there *is* no impact of HC use on weight gain or body weight composition. Most researchers fail to find statistically significant differences in the average weight gain between users and non-users of HCs (see e.g., Mayeda et al., 2014; Rosenberg, 1998). So, why is there such a disconnect between what women report as their experiences and what the results of scientific research find?

The simplest conclusion for scientists to draw from the mismatch between users' experiences and the research results is that the weight gain that women report experiencing while on HCs is being caused by something other than HC use. That is, it is generally assumed that women are misattributing weight gain from other causes to their HCs. However, it may be premature for research scientists and physicians to draw this conclusion without thoroughly examining other, alternative possibilities that could explain women's experiences of weight gain when using HCs. Although some reports from women on changes in body weight from HC use may indeed be spurious, it remains possible that for *some women* taking *some types* of hormonal contraception, the resulting hormonal changes cause physiological, psychological, motivational, or behavioral changes that *do* impact their body weight.

For example, in one experiment (Mayeda et al., 2014), researchers examined body weight and body composition changes among obese and normal weight women who were randomly assigned to use HCs containing either 20 μg ethinyl estradiol | 100 μg levonorgestrel or 30 μg EE | 150 μg levonorgestrel. To measure these changes, they compared participants' body weight and composition prior to- and after- three months of HC treatment. When looking at the mean weight change among both groups of women (obese and normal weight) in response to both doses of HC treatment, there were no differences between women's mean body weight prior to treatment and three months after. These results suggest that HC use has no impact on women's body weight and composition.

However, if you look at the data presented in Figs. 1 and 2 (see Mayeda et al., 2014, pp. 41), it is clear that some women did gain or lose weight after beginning treatment on their assigned HC. Indeed, the authors note in their conclusions that – although the average weight change was small in the overall group and in each subgroup – obese participants and participants assigned to do the lower dose HCs lost a small amount of weight, on average, while the normal weight participants and participants assigned to the higher dose HCs gained a small amount of weight, on average. Although the researchers went on to speculate that these differences likely emerged as a result of regression to the mean, it is possible that at least some of this variation may have occurred as a result of within-woman hormonal changes occurring in response to HC use. Indeed, given the role that female sex hormones play in appetite (Geary, 2004, 2006), feeding behavior (Roney and Simmons, 2017), and metabolic processes (Godsland et al., 1990), it would be surprising to learn that no HCs have any impact on any women's body weight, particularly if the changes were measured over longer spans of time than what is typically captured by many studies or experiments.

Research that draws conclusions of "no effect" without probing into the reasons that some women may experience a side effect that many others do not is the rule rather than the exception in this area of research. The failure to make distinctions among products, users, and time-course has undoubtedly obscured from view important psychological and behavioral effects of HC use that are specific to individual types of products, individual women, or are time course-sensitive. This can give the impression that the impact of HCs on women are minimal and that HC use is more "side-effect free" than it is actually experienced by the women who use HCs. However, there is no reason to expect that all women are going to respond in an identical way to all HCs. Our reliance on average tendencies when reporting on the effects of HCs on women's psychological and behavioral states – particularly when they are created using data from participants known to be heterogenous on dimensions that can impact the measured outcomes – has almost unquestionably led researchers to underestimate the impact of HC use on individual users. For example, for the women in the weight gain study who gained or lost a significant amount of weight on HCs, these changes are significant. This would be true for them regardless of whether they were the only ones to experience this effect, or if enough other women experienced the effect to cause a shift in the mean. The literature suggests that, for some women, changes in body weight are significant enough to impact their decisions to continue or discontinue their HC regimen (Al-Ghashri et al., 2021), which means that they are important to women and therefore important to public health.

Advancing research on the range of effects that women can experience when being treated with HCs will require researchers to move beyond the mean to examine individual differences in women's responses to HC treatment. In our view, this is the most important step researchers can take to make the impact of HC research maximally translatable into clinical practice, and to improve the quality of women's lives. This will require the adoption of research approaches that account for the heterogeneity in women's experiences in ways that go further than accounting for it as "noise" (i.e., controlling for factors known to covary with the predictor or outcome variables and collecting enough data to allow this variance to wash out as error). Instead, it will require researchers to begin to make sense of the heterogeneity in a meaningful way. We must ask: *What are the variables that contribute to women's sometimes very different responses to HC treatment?* Such research will advance the state of knowledge about the effects of specific types of HC treatment on individual women and, ultimately, will allow clinicians to take a more individualized approach toward prescribing HCs to women.

In the paragraphs that follow, we describe areas for future research that we see as being particularly promising in terms of yielding the insights necessary to move toward a precision medicine approach to HC treatment. Specifically, we identify several woman- and HC– specific variables that may play an important role moderating women's psychological and behavioral responses to HC treatment. We follow this

with a discussion of research approaches that offer a great deal of promise in helping researchers account for these variables and maximize the clinical impact of their work. It is our hope that this work will help advance new programs of research that can be used to build the body of knowledge necessary to help develop a precision medicine approach to HC, thereby minimizing the psychological burden of contraception on women.

3. Factors that moderate women's responses to HC use

3.1. Woman-based factors

Health. Among the variables that are most widely recognized as moderators of women's responses to HC treatment is their personal and family health history (World Health Organization, 2015). Indeed, these are often the only person-based factors that are taken into consideration when clinicians recommend to women a specific course of HC treatment. For example, researchers have long known that HC use can increase a women's chances of blood clots and stroke, especially among women with a personal or family history of cardiovascular problems, high blood pressure, obesity, diabetes, or who use nicotine products (World Health Organization, 2015). Accordingly, clinicians prescribing HCs to women reporting one or more of these risk factors choose treatment options that mitigate these risks. For example, clinicians tend to recommend progestin-only HCs to these women, as these products are known to minimize the risk of cardiovascular events.

Although cardiovascular risk factors are critically important for clinicians to incorporate into their HC treatment recommendations, there are many other health-relevant variables that can impact women's positive and negative responses to HC treatment. For example, research finds that factors such as pre-existing iron deficiencies (Stevens et al., 2021) and environmental factors that impact women's nutritional status and endocrine function (Alvergne et al., 2017; Alvergne and Stevens, 2021; Bradley et al., 2009; Mernissi, 1975; Meskele and Mekonnen, 2014) can impact women's moods (e.g., Porri et al., 2021) and responses to HC treatment.

For example, in a study conducted on women living in Ethiopia, researchers found that anemic women (i.e., those who were deficient in iron) were twice as likely to discontinue their use of Depo-Provera (an injectable method of HC) due to negative side effects. Further, they found that this relationship held when controlling for other socio-demographic factors such as age, education, urban vs. rural residence, ethnicity, parity, religion, wealth, and relationship status, suggesting that these patterns are driven by the women's nutritional status and not an alternative, related predictor (Stevens et al., 2021). Others have found similar patterns in women from other developing parts of the world with researchers repeatedly finding that the poorest women in developing countries – who are typically in poor nutritional condition and experiencing suppressed endocrine function – consistently report more side effects of HC use compared to women who are more financially secure (Alvergne et al., 2017; Bradley et al., 2009; Mernissi, 1975; Meskele and Mekonnen, 2014; see Alvergne and Stevens, 2021 for review). Although nutritional deficiencies are less common in more affluent populations, women's experiences with HC side effects are nonetheless likely to vary in response to nutritional status and health.

Similarly, we currently know very little about the role that women's body weight plays in contributing to the likelihood of experiencing side effects while on HC treatment. This is a potentially important moderator of women's experiences with HCs since all methods administer a standard dose of synthetic hormones to women, regardless of body weight. Accordingly, the impact of this standard dose may be more experientially noticeable to women with lower body weights than those with higher body weights. Although due diligence has been done researching the moderating effect of body weight on HC efficacy (see Gupta and Forest, 2008 for a brief review), almost nothing is known about body weight as a moderator of women's experiences with HC side effects (with some exceptions, see Talwar and Berger, 1977), making this an important target of future research.

Duration of Use and Time Course. The impact of HCs on women's psychobehavioral outcomes appears to be moderated by both the timing during which HC use first occurs (e.g., adolescence versus adulthood), but also by the duration of HC use. While women frequently experience side effects of HC use when they first begin use, some research suggests that these effects may diminish over time as women's bodies adjust to the hormonal changes initiated by HCs. For example, research suggests that many side effects – such as breakthrough bleeding and acne – tend to decrease in severity or disappear after the first 3 months of HC use (Barr, 2010). It is likely that some of this pattern can be accounted for by the so-called survivorship effect, which describes the phenomenon wherein women whose HC side effects are intolerable discontinue use, giving the false impression that negative side effects are decreasing over time. However, it is also possible that HC using women experience some level of physiological adaptation to the hormonal milieu created by HCs that causes them to feel better as their bodies adjust.

The idea that women's bodies may adjust to the hormonal changes initiated by HCs in ways that change their side effect profile is particularly likely for women who use a hormonal IUD. While OCs, the implant, and the HC shot each prevent pregnancy primarily through the continuous suppression of the HPG axis thereby preventing ovulation, many women who use a low dose hormonal IUD often begin to ovulate again after a year or more of use (Bayer HealthCare Pharmaceuticals Inc., 2021). Given that ovulation is accompanied by cyclicality in endogenous hormone production, women who have been on a low dose hormonal IUDs for over a year are likely to be more hormonally similar to NC women than they are to women taking alternative forms of HC. As such, the duration of HC use is particularly important to account for in studies including women using hormonal IUDs, as their side effect profile could possibly change quite dramatically after ovulation resumes.

To this day, little research has been done to examine the long-term effects of any type of HC use on women's psychobehavioral outcomes. Given that many women begin HC treatment in their teens and twenties and then remain on HCs for sometimes several decades, this is an important area of needed research. Does being on HCs for a prolonged period of time impact women's ability to adapt back to their endogenous hormone production once they discontinue use? How does prolonged HC use impact nervous- and endocrine- system function? Brain aging? Given the important role of female sex hormones in modulating the risk for neurodegenerative diseases (Mosconi et al., 2017) and brain aging (de Lange et al., 2020), these questions are of great importance for researchers to consider in their future work.

Women's Personal and Family Mental Health History. Although we still know relatively little about the impact of women's personal- or family-mental health histories on women's responses to HC treatment, a growing body of research suggests that they may matter. In particular, this research finds that factors such as a woman's personal- and family-history of experiencing outcomes such as depression, mental illness, or mood-related side effects in response to HC treatment may each moderate how women themselves respond. For example, researchers find that women with a history of depression or mental illness (DeSoto et al., 2003; Kutner and Brown, 1972; Lundin et al., 2017; Oinonen and Mazmanian, 2002) or a personal or family history of mood-related side effects on HCs (Gingnell et al., 2013) may be more likely to experience mood related side effects on HCs. In one double-blinded, placebo-controlled trial, researchers found that women who had previously experienced emotional side-effects on HCs responded to oral contraceptive (OC) treatment with higher scores of depressed mood, mood swings, and fatigue than what was found in controls or similar women given a placebo. Others have found similar effects among women with a history of pregnancy-related mood symptoms, a family history of HC side effects, and among women who are postpartum (Oinonen and Mazmanian, 2002).

It is vital to consider, however, that other research finds the opposite pattern, demonstrating that for some women with a history of mood- and mental health- disturbances, HC use can be therapeutic. For example, some research indicates that HC use can stabilize mood in women with bipolar disorder (Rasgon et al., 2003), and for years, researchers have noted that HC use can have therapeutic, mood-stabilizing effects for women with PMS (Apter et al., 2003; Freeman et al., 2001; Schultz-Zehden and Boschitsch, 2006; Short, 2009) and premenstrual dysphoric disorder (PMDD; Cheslack-Postava et al., 2015; Lopez et al., 2012). Women's personal and family histories with any of these conditions could therefore serve as important moderators of women's responses to HC treatment, with these factors leading to improved outcomes in some cases, and worse outcomes in others. Indeed, it would be surprising to find that women's personal histories with other outcomes that appear to be non-uniformly impacted by HC treatment – such as changes in sexual function and body weight – weren't also affected by women's personal- and family-histories of sexual dysfunction and body weight fluctuations (e.g., sexual function: Both et al., 2019; Smith et al, 2014; weight composition: Gallo et al., 2014; Lopez et al., 2016). Future research would benefit from including such measures to see whether they help account for what looks like, on the surface, idiosyncratic differences between women in their responses to HC treatment.

Genetics. The body of research demonstrating differences in women's responses to HCs based on family and personal health history is growing (see research reviewed above). Currently, much less is known about whether women's different responses to HC treatment are affected by genetic differences that impact areas of the nervous system affected by HC treatment. However, these genetic differences are likely to play an important role in characterizing and explaining some of the observed differences between women in response to HC treatment. For example, researchers have identified specific genetic polymorphisms that impact the density of each sex hormone- and neurotransmitter-receptors, as well as their sensitivity and functioning (see Cariaso and Lennon, 2012). These differences are likely to impact the ways that women experience the hormonal changes created by HCs, thereby playing a role in accounting for some of the observed variability in women's responses to HC treatment. Indeed, although very few studies have investigated the impact of gene-based differences in how women respond to HCs, the research that has been conducted in this area suggests this will be a fruitful area of inquiry.

For example, in one study, researchers found that women who have genes that code for a specific type of mineralocorticoid receptor seem to be protected from some of the negative psychological changes that women can experience on HCs. In particular, these researchers found that women who carry mineralocorticoid receptor haplotype II (but not haplotypes I or III) seem to be protected from some of the psychological changes exhibited by HC-taking women that are linked to anxiety and depression (Hamstra et al., 2016). This indicates that this genetic factor may play a role in women's positive or negative experiences on HC treatment, making it a useful variable for clinicians to consider as they develop personalized HC treatments.

Similar gene-dependent results are also beginning to emerge in research examining the association between HC use and the development of sexual side effects. For example, some researchers have found that women's experiences with sexual side effects while on HCs are moderated by genes associated with androgen receptor efficiency (Goldstein et al., 2014). Women with more efficient receptors appear to have fewer side-effects. Although research into the moderating role of genes in women's responses to HC treatment is still in its infancy, results such as these suggest that testing for genetic polymorphisms that impact how women's bodies respond to and metabolize hormones may be a particularly fruitful avenue for future research targeted at developing a personalized medicine approach to HC treatment. Future research would benefit from beginning to explore these issues in further depth, with particular attention being given to genetic differences in regions of the genome known to play a role in factors such as hormone and neurotransmitter receptor density, efficiency, and plasticity.

Women's Biological Milieu Prior To HC Treatment. Another related, but conceptually-distinct, candidate moderator of women's experiences on HCs is that of her pre-existing biological milieu. That is, it is likely that women's positive or negative experiences with HC treatment are affected in important ways by factors such as a woman's hormone and neurotransmitter levels prior to HC use, as well as the density and efficiency of her hormone and neurotransmitter receptors. For example, given that HC treatment inhibits the activities of the HPG axis by keeping levels of synthetic progesterone (i.e., progestins) high, one potentially fruitful avenue of research would be to examine whether women's endogenous levels of estrogen and progesterone in the luteal phase prior to HC treatment moderate women's response to different doses of HCs. Do women who produce, on average, higher levels of endogenous sex hormones during the luteal phase experience fewer HC side effects on higher dose treatments than women who tend to produce lower levels of endogenous hormones? And vice versa for low dose treatments?

Questions such as this – as well as those aimed at exploring other facets of women's pre-treatment biological states – promise to yield needed-insight into some of the between-woman variability exhibited in responses to HC treatment. Although some of these research questions can be studied using human participants (e.g., those looking at pre-existing hormone levels), others are better suited to research conducted using non-human animal models (e.g., those looking at hormone receptor density, and how modifications of hormone receptor density impact HC-related outcomes). Further, it is important to note that assessing women's pre-HC treatment hormonal milieu – whether for research or clinical purposes – can be difficult to assess given the tremendous cycle-to-cycle variability that can occur in individual women's cycles (see e.g., Jasienska et al., 2017). Accordingly, research (and treatment plans) based on woman-based differences in pre-existing hormone levels will first require the development of novel measurement protocols that are able to account for this variability, while still being able to identify stable individual differences in average hormone levels.

History of Childhood Trauma. Research has long found support for the idea that a person's early life environments have a lasting impact on how they respond to various environmental triggers encountered in adulthood (see e.g., Crandall et al., 2019; Cunningham et al., 2022; Griskevicius et al., 2011; Ellis et al., 2003; Mengelkoch and Hill, 2020; Miller et al., 2011). Although very little is known about the impact of women's early life environments on their responses to HC treatment, several studies have found evidence that exposure to childhood adversity moderates women's responses to the hormonal changes that occur across a typical menstrual cycle. It is therefore possible that these exposures may also have implications for women's responses to HC treatment.

For example, research finds that women who have been exposed to childhood maltreatment exhibit a significantly greater risk of suffering from hormonally mediated syndromes such PMS and PMDD (see e.g., Bertone-Johnson et al., 2014; Ito et al., 2021; Koci and Strickland, 2007). This suggests that early life exposures could play a key role in factors such as hormone and neurotransmitter receptor plasticity, which impact women's ability to functionally adapt to hormonal changes occurring across the cycle and possibly in response to HC treatment (see e.g., Schweizer-Schubert et al., 2021). In one large prospective longitudinal study, for example, researchers examining the association between early life abuse and subsequent development of PMS found that women reporting severe childhood physical or emotional abuse had a more than 200% increased risk of developing PMS than those without this history. The researchers found that these associations held after controlling for multiple other factors that could contribute to the association between these variables, such as childhood social support (Bertone-Johnson et al., 2014).

This body of work, although it does not address the issue of HCs specifically, demonstrates that the relationship between the activities of

women's endogenous sex hormones and mood may be moderated by exposure to early life trauma. The hormonal modifications that occur in response to HC treatment may have a similar impact on women with early stress exposures, increasing their vulnerability to negative side-effects, particularly those related to mood. Future research would benefit from examining these possibilities, as well as others, including whether exposure to early adversity also moderates the demonstrated effect of HCs on the functioning of the stress response and structural changes in the hippocampus, both of which are known to occur in response to each HC use (Kirschbaum et al., 1999; Kumsta et al., 2007; Lovallo et al., 2019; Merz, 2017; Nielsen et al., 2013; Pletzer et al., 2019; Rohleder et al., 2003; Roche et al., 2013) and exposure to early life trauma (Bunea et al., 2017; Dahmen et al., 2018; Rao et al., 2010). In addition to providing important new insights into the (possible) associations between women's developmental histories and responses to hormonal changes in adulthood, such work would help women's healthcare providers make more informed contraceptive recommendations to women who have experienced trauma.

Current Stress. As noted, research indicates that HCs (at least some generations of HCs) can impact the functioning of the HPA axis. Accordingly, it is possible that some of the observed heterogeneity in women's psychological responses to HC treatment might emerge from an interaction between the stress-like modifications to the HPA axis that can occur while using HCs combined with women's experiences with acute stress while using HCs. This is because psychosocial stress affects both the functioning of the HPA axis and numerous psychosocial outcomes known to be affected by HC use, including sexual functioning (e.g., libido, sexual satisfaction), physical health (e.g., body weight, inflammatory activity), and mood. Undesirable changes in any of these outcomes could therefore emerge as a result of chronically dysregulated responses to acute psychosocial stress occurring during the time of HC use.

Indeed, a large and growing body of literature finds evidence that individuals' whose HPA axes have been blunted through exposure to chronic stress (compared to those who have not) exhibit exaggerated inflammatory activity (Cohen et al., 2012; Miller et al., 2008, 2011), a greater risk of anxiety and depression (Tabak et al., 2016; Slavich and Irwin, 2014; Slavich and Sacher, 2019), and emotional dysregulation (Bradley et al., 2011) in response to acute stress. It therefore stands to reason that women whose HPA axes exhibit similar blunting in response to HC use may respond similarly in response to acute stress. Research is therefore needed to examine whether women's exposures to acute stress at the time of HC use interact with the HPA axis modifying effects of HCs to impact women's experiences with side effects. Such research could shed novel insights into the mechanisms behind some women's negative psychological responses to HC use.

Age and Age at Onset of Use. Emerging research suggests that the age at which women begin using HCs may have a lasting impact on their experiences with mood-related side effects. The best evidence of this association comes from the large, nationwide study of the links between HC use and the development of mood disorders that was conducted using health records from more than one million Danish women between the ages of 15 and 34 described earlier in this review (Skovlund et al., 2016). The researchers found that HC use was associated with a significantly greater risk of being subsequently diagnosed with depression for women of all ages. However, when they included age as a moderator of their results, they found that this risk was being asymmetrically shouldered by the adolescent women (women ages 15–19) in their sample. The researchers found that the risk of developing depression for women using non-oral HCs was up to three times higher for adolescent women than it was for the adults in their sample using the same products. These results highlight the importance of considering age of onset of HC use as a moderator in research examining the impact of HC use on psychobehavioral outcomes and further highlights that the potential for adolescent girls to experience mood-related side effects when using HCs should also be considered carefully by clinicians prescribing HCs to women and girls for reasons other than pregnancy prevention (i.e., acne control, period management).

Although the mechanisms through which adolescent girls are at an exaggerated risk of developing depression from HC use are relatively unknown, much research implicates female sex hormones in the etiology of depression (Jacobs et al., 2015). Inhibiting the release of cyclically fluctuating endogenous sex hormones and replacing them with a steady dose of synthetic hormones in young women whose brains are still developing could therefore have a profound and lasting impact on the development of stress and emotional reactivity systems in the brain. Indeed, recent research finds that HC use in adolescence predicts an increased risk of depression in adulthood – even among those who are no longer using HCs – when compared to women who have never used HCs and those who are current users, but didn't begin use until adulthood (Anderl et al., 2020).

Emerging research also suggests that adolescent HC use may have a lasting impact on the functioning of the HPA axis and women's acute cortisol reactivity to stress. For example, in one study (Sharma et al., 2020), researchers classified women as either cortisol responders or non-responders based on the magnitude of their stress response to an acute stressor. Those who exhibited a robust cortisol response were labeled "responders", and those without such a response were labeled "non-responders". The researchers observed that the category women fell into was moderated in important ways by their history of HC use. In particular, they found that 53% of women who began using HCs in adulthood were cortisol responders, while only 19% of women who began using HCs in adolescence were cortisol responders. These results suggest that women who began HC use in adolescence of are less likely to exhibit a typical cortisol response to stress compared to those who began HC use in adulthood. Such a pattern is clinically relevant, as dysregulated cortisol responses to stress have been found to be a risk factor for depression and anxiety disorders (Fisksdal et al., 2019).

Research studies such as these suggest that HC use during adolescence may have a lasting impact on women's nervous and endocrine systems, changing their risk of developing mood-related disorders. As this research is still in its infancy, additional research is needed to understand the full spectrum of these consequences, allowing women and their clinicians to make more informed decisions about prescribing HCs to young women and girls, particularly for reasons less serious than pregnancy prevention (e.g., to manage acne, menstrual cycle irregularities).

3.2. *Prescription-based factors*

HC Type. As described above, not all forms of HCs are created equally and, as a result, not all forms of HCs impact women in the same ways. HCs vary in their composition, with combination OCs containing both ethynyl estradiol and a progestin, and progestin only products – which come pill form, as well as in the form of a shot, implant, and IUD – containing only a progestin. The variability among these products is compounded by the fact that they can contain different types of progestins, which vary based on their chemical composition. Accordingly, their impact on women's hormone receptors may be different and this may impact women's responses to different HCs.

In one study, for example, researchers found that HC type moderated women's experience of sexual side effects. In particular, they found that women using combined OCs exhibited no impairment in sexual functioning while using HCs, while women using progestin-only injectables and progestin only pills did (Hassanin et al., 2018). Given the important role of estradiol in NC women's sexual desire (Roney and Simmons 2013; 2016; Shirazi et al., 2019), it is unsurprising that progestin only methods of HCs are associated with decreased sexual functioning. Indeed, failure to account for HC product type in research examining the impact of HCs on sexual function may be responsible for some of the inconsistencies in this literature (see e.g., Heiman et al., 2011). For example, there is reason to expect that women using a hormonal IUD, for

whom ovulation has resumed, would have fewer sexual side effects than women on an OC, for whom ovulation continues to be suppressed. Future research would benefit from carefully considering and accounting for the variability in HC product type on women's responses to HC treatment. Such differences likely play a profound role in women's experiences with HCs and understanding which types of HC treatments minimize specific types of side effects is a necessary next step in the development of a precision medicine approach to HC treatment.

Progestin Type. Although the various forms of HCs available on the market differ from one another in a variety of ways, among the most meaningful of these differences is the types of progestins they use. Progestins are typically grouped according to their generation, which is a designation given to them based on when they first became available on the market (e.g., first generation progestins being the first available on the market, those containing second generation HCs were the second to be made available, and so on).

All four generations of progestins are currently in use, which means that any sample of women who are current users of HC is likely to be comprised of women on several different types of products, using all four types of progestins. These differences can have an important impact on how women respond to HC treatment because each type of product conveys a slightly different hormonal message within women's bodies (e.g., Louw-du Toit et al., 2017) (see Box 2 for more information on progestin types). For example, research finds that women on first and second generation HCs – which are more androgenic than subsequent generations of HCs – often experience a greater number of masculinizing side effects, such as acne, hirsutism, and scalp hair loss, than women on later generations of products (Jones, 1995). Others have found that the progestin generation in women's HCs moderate their impact on women's sleep quality (Bezerra et al., 2020), sexual function (Shahnazi et al., 2015), and the responsiveness of the HPA axis to stress (Herrera et al., 2019). For example, in one study, researchers found that women using OCs containing first and third generation progestins exhibited a blunted HPA axis response to acute stress, whereas women using OCs containing second generation progestins were spared from this effect, exhibiting normal HPA axis function (Herrera et al., 2019).

Box 2. Different types of HCs.

Type of Progestin	HC Type and Progestin Generation	Androgenic and Progestational effects	Metabolic Half-Life
Norethindrone/ Norethisterone acetate	1st gen oral HC; hormone therapy	Moderately androgenic, modertaely progestational	34.8 h
Ethynodiol acetate	1st gen oral HC; hormone therapy	Low androgenicity, highly progestational	N / A
Medroxy-progesterone acetate	Depo-Provera (injectable); 1st gen HC; hormone therapy	Moderate- to highly androgenic, highly progestational	40 – 60 h
Levonorgestrel	2nd gen oral HC; Hormonal IUD; emergency contraception	Highly androgenic, highly progestational	26 h
Norgestrel	2nd gen oral HC; hormone therapy	Highly androgenic, highly progestational	21 h
Desogestrel / Etonogestrel	3rd gen oral HC; Nexplanon (implant); Nuva Ring (insertable); hormone therapy	Low androgenicity, highly progestational	23 – 25 h
Gestodene	3rd gen oral HC; hormone therapy	Low androgenicity, highly progestational	12 – 15 h
Norgestimate	3rd gen oral HC; hormone therapy	Low androgenicity, highly progestational	12 – 30 h
Drospirenone	4th gen oral HC; hormone therapy	Anti-androgenic and little progestational activity	30 h
Dienogest	4th gen oral HC; hormone therapy	Anti-androgenic and little progestational activity	10 h

Note: gen = generation; HC = hormonal contraceptive.

Classifying different types of HCs by the generation of progestin they contain allows researchers to investigate differences in how women respond to HC treatment based on the composition of the products they are using without creating such small groups within HC users that it would be difficult to gather large enough samples to investigate meaningful differences between women using different HC types. However, this categorization is still somewhat crude because, although progestins within the same generation are more similar to one another than they are different, they can still differ in important ways that impact women's responses to them.

For example, there is some evidence that suggests that progestins of the same generation might exhibit important differences in their androgenicity, particularly among those categorized as first generation (Dickerson et al., 2002). Further, different progestins within the same generation can differ quite dramatically in terms of their metabolic half-life. As noted in Box 2, Dienogest and Drosperinone are both anti-androgenic fourth generation progestins; however, their metabolic half-lives are respectively 10- and 30- hours. These differences can have an important impact on women's experiences with HC treatment. Research suggests that the androgenicity of women's HC treatment plays an important role in driving structural and functional differences observed in the nervous systems of HC users compared to non-users (Pletzer et al., 2015). Further, the metabolic properties of a medication can impact the longevity and severity of its side-effects (Mangoni and Jackson, 2004). Accordingly, although the categorization of progestins based on their generation is clinically supported (see e.g., Practice Committee of American Society for Reproductive Medicine, 2008) this may obscure functionally-relevant differences between progestins within the same generation.

3.3. Recommendations for research approaches to help advance a precision medicine approach to HCs

Conducting precision research on the links between HC use and women's psychological and behavioral experiences is clearly a necessary first step to advance a precision medicine approach to HC treatment. However, conducting precision research creates a number of unique challenges that are not present when researchers take a more traditional approach to studying the psychobehavioral correlates of HC use. For example, a researcher seeking to examine whether possession of a specific genetic haplotype moderates the impact of third-generation progestins on women's moods would either need to a) test her hypothesis on a very large sample to ensure that she has recruited enough women from the target group(s) or b) implement a time-consuming targeted recruitment procedure aimed at selecting only women who meet the study's needs as participants. Further, if this research is to have a meaningful clinical impact on the HC treatments offered to women, researchers need to take steps to ensure that their research has visibility outside their immediate area of specialization, and is made available, understandable, and actionable to women and their physicians. Hurdles such as these can make this research seem insurmountably difficult and expensive to conduct, causing researchers to shy away from these important and necessary research questions.

In the following sections, we make recommendations for research

approaches that can be used to help create the body of knowledge necessary to advance development of a precision medicine approach to HC treatment. First, we discuss methodological considerations and data collection opportunities for researchers interested in conducting precision research on the psychobehavioral correlates of HC use. We follow this with a discussion of ways that researchers can make their research maximally visible and translatable to a clinical setting. See Box 3 for a summary of our recommendations.

3.4. Experimental research

Experimental research is the gold-standard for establishing that a cause-and-effect relationship exists between two variables, making experiments an important tool in the development of research to help advance a precision medicine approach to HC treatment. Not all experimental designs are created equally, though, and each present their own advantages and challenges in the context of HC research.

Box 3. Areas for promising HC-related research.

Potential Moderators of women's responses to HCs	Examples of research questions
HC type	Does the generation of HC used moderate relationships between HC use and perseverance on cognitively taxing tasks?
Age of HC onset	Does age of first HC use moderate the impact of HC use on sexual function?
Duration of HC use	Does duration of HC use moderate the effect of HC use on emotional memory?
Genetic	Do certain SNPs moderate relationships between HC use and mood?
Lifestyle	Do women who exercise regularly report better outcomes on some types of HCs compared to others?
Biological	Do women who produce higher levels of endogenous sex hormones during the luteal phase experience fewer HC side effects on some HC treatments than women who produce lower levels of endogenous hormones?

Note: HC = hormonal contraceptive.

4. Double-blind, Placebo-Controlled clinical trials

A double-blind, placebo-controlled clinical trial – in which HC prescription is manipulated and a specified outcome is measured – is the ideal experimental design for those seeking to understand the impact of HC use on women. By allowing the researcher to manipulate factors such as HC type, dosage, and mode of administration, researchers can exercise control over some of the biggest sources of between-person heterogeneity that emerge in most cross-sectional designs. Double-blinding prevents researcher bias in researcher-participant interactions and using a placebo control group ensures that any effects that are discovered are result of HC treatment, *per se*, and not the result of believing that one is being treated by HCs. This makes these sorts of studies a very powerful tool in understanding the psychobehavioral effects of HC use.

For example, in one experiment, researchers examined the impact of a levonorgestrel-containing combined OC on women's mood and reactivity in the emotional circuitry of the brain (Gingnell et al., 2013). Researchers recruited a sample of women who reported having previous experience with mood-related side effects on OCs. After three weeks of treatment, the researchers found women randomly assigned to the OC condition reported more depressed mood and mood swings, compared to those randomly assigned to the placebo condition. Additionally, these mood-related outcomes were accompanied by altered right amygdala and left insula reactivity to emotional stimuli during an fMRI emotional processing task. This careful, controlled design provided the researchers confidence that the differential outcomes experienced by the OC and placebo groups of women were *caused* by OC use. Additionally, this example highlights the importance of implementing research designs which are well-designed to find an effect. The experiences of these women who had negative outcomes as a result of HC use would likely have been overlooked if the researchers had, for example, recruited a sample of women who had only experienced positive outcomes from previous OC use, or who had no experiences with previous OC use. While the sample size in this study was smaller than would be ideal ($n = 34$), this work provided the strongest evidence at its time of publication that OC use *causes* negative mood in some women.

Despite their strengths, double-blind, placebo-controlled clinical trials can be costly and difficult to conduct. This has undoubtedly led some researchers to avoid this type of design and important area of research out of practical concerns. However, experimental designs that do not use double-blinding and placebo controls – or that use non-human animal models as subjects – can still provide many valuable insights to researchers. We discuss these next.

4.1. Non-human animal models

One particularly fruitful approach for researchers hoping to better understand person- and HC type-based differences in how women respond to HC treatment is to conduct experiments using non-human animal models. Such an approach allows researchers to manipulate or control hypothesized sources of between-user heterogeneity in responses to HC, making it an important tool in our ability to test hypotheses about the causal links between these sources of heterogeneity and their association with user-specific outcomes. Further, research using these models allow researchers to investigate the effects of HCs on neurobiological processes that cannot be examined in humans (e.g., gene expression in different regions of the brain). Indeed, research using non-human animal models has provided invaluable insights into the effects of HCs on: neurotransmission (i.e., levels of gamma-aminobutyric acid [GABA], expression of $GABA_A$ receptors, serotonin levels, dopamine levels [Baker et al., 1977; Daabees et al., 1981; Follesa et al., 2002; Sassoè-Pognetto et al., 2007]), and expression of brain derived neurotropic factors (BDNF; Simone et al., 2015). For a review of such research, see Porcu et al., 2019.

Research using non-human animal models is particularly well-suited to uncovering the mechanistic actions driving effects of HCs in women, as well as their links to behavior (e.g., changes in anxiety-like behaviors: Follesa et al., 2002; Picazo et al., 1998; Simone et al., 2015. Although insights about the impact of HC use on women derived from research on non-human animals need to be interpreted with caution (we cannot assume that human females will respond the same way as female rats or mice), such research represents a critical step in the development of the knowledgebase necessary to advance a precision medicine approach to HC treatment. Further, such research is particularly powerful when paired with experimental or cross-sectional research using human participants to test for complementary results. There is a lot to be learned from such collaborative work and it is our hope to see a greater number of such collaborations in the coming years. Such collaborations promise to offer critical new insights into the impact of HC use on the structure and function of female nervous system, and how these changes are experienced by the women who use HCs.

4.2. Within-subjects pre- vs. post- quasi-experimental designs

One of the conditions necessary for an experiment is random assignment. That is, experiments require that participants are randomly assigned to different experimental conditions. This can be difficult to do when conducting research aiming to investigate the impact of HC use on women, as randomly assigning one woman to HC treatment and another to a non-contraceptive placebo can put those in the latter group at a high risk of unplanned pregnancy. Quasi-experimental designs, although they cannot be used to make cause-and-effect claims about the measured impact of HC use on women, can nonetheless be a powerful tool for uncovering the links between HC use and researcher-specified

outcomes. Among these designs, one of the most powerful is the multiple time-point, within-subjects quasi-experimental study. In such a study, researchers measure women before and after HC treatment, allowing each participant to serve as her own NC control group. Researchers then compare women's baseline measures taken prior to HC treatment and to those taken after 2–3 months of HC use to see how HC use changes women's responses. If women's scores change in response to treatment, this supports the hypothesis that HC affects the outcome. If women's scores are the same, this supports the hypothesis that they do not.

In one example of a study using this type of within-subjects design, researchers investigated how OC use impacted women's preferences for masculinity in male faces (Little et al., 2013). The researchers recruited a sample of NC women, some of whom were interested in using OCs. Researchers then tested the participants' preferences for masculinity in male faces twice – once at the beginning of the study when the women were NC, and then again after about three months of OC use – and found that, within women who began using OCs, women preferred more masculine faces before using OCs compared to after.

This type of quasi-experimental, within-subjects design can provide strong evidence for the association between HC use and specified psychobehavioral outcomes. However, the recruitment of such a cohort can still be time-consuming, and, in longitudinal designs, participant attrition between the baseline and follow-up assessments can reduce the total sample size, wasting researcher time and resources. This type of design can also lack a mechanism to control for effects of time, as it is possible that differences between women's baseline and follow-up assessments are the result of HC use, time, an interaction between these variables, or some additional external variable not accounted for by the researcher. Nonetheless, such studies represent a powerful tool for researchers hoping to better understand the impact of HC use on women, particularly on variables that are expected to change over time.

4.3. Naturalistic and between-subjects quasi-experimental designs

Experimenters often avoid the logistical complications involved in true experimental designs and longitudinal research by using naturalistic and quasi-experimental designs. In these designs, women who are already using HCs constitute the HC group, and women who are currently NC constitute the NC group. These groups are then compared to see whether they differ between one-another on dimensions that are being measured by the researcher. Such research is generally able to capture a larger sample of women and can therefore be generalized to a broader population compared to some of the more controlled designs we have discussed above. The main concerns with this type of design are related to self-selection, however. Women who choose to be on HCs can be different from non-HC users on dimensions related to the research question, making it difficult to interpret the results of such research. Any differences that are found between HC and NC women could be the result of HC use or could be the result of other factors, such as the desire to be sexually active without becoming pregnant, openness to medications, access to medical care, or any number of additional factors that separate users of HCs from non-users.

A second limitation of using naturalistic designs is that they can mask negatively-experienced effects of HC use due to the survivorship bias. The survivorship bias describes the fact that women who are active users of HCs are comprised only of women whose side effects were tolerable enough to continue treatment. These samples do not include women whose side effects were intolerable, causing them to discontinue use. Accordingly, even a perfectly randomly sampled group of women using HCs will be biased, containing more women who have experienced positive outcomes when using their current HC method than women who have experienced negative outcomes. Clearly, survivorship bias in a major concern for any researchers interested in investigating any negative outcomes which could be caused by HC use when using naturalistic (and many longitudinal) experimental designs. While self-selection and survivorship bias are important limitations for researchers to consider when interpreting the results of such research, they shouldn't overshadow the benefits of naturalistic designs. Naturalistic experiments can be quickly and relatively easily conducted and, as such, are the ideal way to explore early hypotheses, or to determine the generalizability of effects in broad populations.

4.4. Taking advantage of big data

The rise in the number of women's health applications and services such as Nurx (an online vendor for hormonal contraceptives), Flo (a digital cycle tracking application), and Tuune (a hormonal wellness health application) provide a unique opportunity for researchers examining the range of effects that HC use can have on women. Having access to data from tens or hundreds of thousands of women allows researchers to get around the primary hurdle they encounter when studying the associations between certain types of HCs on certain types of women: small sample sizes. Partnering with companies with large user databases can allow researchers to examine associations between specific types of HC use and recorded user outcomes in ways that are not feasible with researcher-collected data.

In addition to data available from health applications, there are also a number of public health registries, such as those available in Sweden and Denmark, which have been successfully used to examine the links between different types of HC use and outcomes such as depression (Lundin et al., 2021; Skovlund et al. 2016) and suicide risk (Skovlund et al., 2018). Data from such sources – because they are collected on the entire population – are large enough to assess even very rare outcomes (e.g., suicide) and also to examine the associations between specific types of HC use and these rare outcomes.

For example, in one recent study, researchers were able to examine the association between specific types of HC use and suicide risk in both adolescent and adult women (Skovlund et al., 2018). The results of this study found that HC use (vs. non-use) was positively associated with a first suicide attempt, particularly in adolescent women. Further, the researchers found that the HC patch, vaginal ring, and progestin-only products were associated with higher risks than oral combined products, and that the relative risk of suicide attempt rose twofold one month after beginning HC treatment and remained high until after one year of use. Although research using big data that are collected by third parties can be limited in terms of only being able to analyze the data collected by the third party (which is not always the data that would be ideal for answering the specific questions the researcher has in mind), it can be a powerful accompaniment to research conducted using data collected firsthand by the researcher.

4.5. Longitudinal research

Some of the most urgently-needed research on HC use is research concerning time-course effects. As noted above, little is currently known about whether the impact of HC use on women's psychobehavioral outcomes differs depending on the age of onset of HC use, the duration of HC use, or how these effects change over time with continued HC use. Although there are multiple potential ways to address these questions empirically, the most powerful way to address such research questions is through the use of longitudinal research. Unfortunately, researchers do not often employ longitudinal designs, in part because longitudinal studies are time consuming, expensive, difficult to conduct and manage, and likely to suffer from attrition. Further, this attrition may not be random, as the survivorship bias likely means that women who do not complete the study are the women most likely to suffer from negative side effects. As such, many researchers use single time point, cross-sectional studies to compare women taking HCs to those who are NC. While cross-sectional results are useful, they may mask important within-women effects and individual differences which contribute to important outcomes and limit our understanding of how HCs actually impact women's experiences.

For example, as noted above, multiple studies seem to indicate that side effects may be worse for women during the first three to twelve months of HC use. However, these sorts of time-course data are rarely recorded and the precise mechanism responsible for this pattern (if this pattern indeed exists) is unknown. Research into these issues will be an important next step in being able to provide women with a prognosis for their HC user journey. Further, it will provide researchers with needed insight into the mechanisms by which HCs affect users, including insight into the ways that women's bodies adapt (or don't adapt) to the repeated administration of exogenous hormones.

Longitudinal research is also necessary to examine the effects of long-term HC use on women. How do women's nervous and endocrine systems respond to the long-term suppression of HPG axis? And what is the time-course of the reversal once women discontinue HCs? That is, how long does it take women to "return to normal" after ceasing HC use? Although ovarian activity is believed to resume for most women within 2–6 months of HC cessation (Harlap and Baras, 1984; Van den Berg et al., 2010), little is known about this transition or how it differs between women or across systems known to be impacted by HC use. For example, research finds that levels of sex hormone-binding globulins (SHBGs) remain elevated in former users of HC for at least 6 months after HC cessation (Panzer et al., 2006). This suggests that the various biological modifications that occur in response to HC treatment may have different timelines for recovery. Understanding whether- and how-women's bodies adjust "back to normal" is important for women to understand when making decisions about transitioning both on and off of HCs.

4.6. Registered clinical trials

One of the primary frustrations that women have with HCs is that they feel poorly informed about the range of psychological side-effects that are possible from use. Oftentimes, this information isn't shared with women by their physicians because the physicians in charge of their care have little-to-no exposure to research being conducted in behavioral neuroscience and neuroendocrinology. The result is that there is much research knowledge that has accumulated over the last several decades on the associations between HC use and changes in psychological states that is not being shared as part of the patient education that is given to women who are being prescribed HCs.

Unfortunately, the issue of cross-disciplinary invisibility is an issue that is endemic in science. This so-called "silo effect" refers to the tendency for researchers to become entrenched only in the ideas of their home discipline (whether medicine, psychology, neuroscience, anthropology, etc.) and to lack awareness of the research being conducted in other, related disciplines. In addition to slowing the speed of new discoveries by creating redundancy in theories and research results, the silo effect prevents the development of a holistic understanding of the topics being investigated, including topics related women's psychological functioning and HC use. Because the field of medicine resides in one knowledge silo, and neuroscience and psychology reside in another, physicians and the even the academics who train them have little awareness of the research being conducted on the associations between HC use and psychobehavioral outcomes.

Despite knowledge silos being endemic to research science, researchers in psychology and neuroscience can increase the visibility of their research to women and the physicians who serve them by registering their research as clinical trials. Although many registered clinical trials are conducted to examine issues related to a drug's safety and efficacy prior to a drug's approval by the FDA (the focus of Phase I, II, and III trials), Phase IV trials explore issues related to drugs that have already been approved by the FDA, including issues related to understanding the range of a drug's side effects. Accordingly, much of the research being conducted by psychologists and neuroscientists examining the psychobehavioral consequences of HC use would qualify as a Phase IV trial. In addition to increasing the visibility of this research, conducting registered clinical trials helps ensure transparency in the science by making the predictions being tested publicly available. Additionally, registering research as a clinical trial makes available to researchers the option of publishing their research in a medical research journal, per the requirements of the International Committee of Medical Journal Editors (ICMJE).

Because registering a research study as a clinical trial is an unfamiliar practice to many researchers outside of clinical psychology, it may seem to be somewhat daunting prospect. However, the process of registering research as a trial is similar to the process of pre-registering research hypotheses on platforms such as the Open Science Framework (OSF) and does not require that the registered research be a double-blind, placebo-controlled experiment. Indeed, much of the research conducted by the readership of this special issue is likely appropriate for consideration as a Phase IV trial, particularly if the outcome in question has bearing on health or quality of life. There are a number of resources available for researchers looking for assistance getting their research registered as a clinical trial, including web-based registration tips (including this one by the National Institutes of Health: https://clinicaltrials.gov/ct2/manage-recs/how-register) and books (see e.g., Friedman et al., 2015). Although registering research as a clinical trial does not guarantee visibility to researchers in the medical community, it opens up the possibility of publishing the research in journals that are read by healthcare professionals and increases the probability that it will be encountered by those in the public and operating in a clinical setting.

Box 4. Summary of Research Recommendations to Advance a Precision Medicine Approach to HCs.

1. When possible, employ double-blind, placebo controlled, clinical trials, where HC prescription is the independent variable being manipulated
   - If your research question(s) cannot be addressed feasibly with human models, consider utilizing non-human animal models
   - When possible, conduct within-subjects, experimental research, taking advantage of longitudinal designs
   - If experimental, longitudinal designs are not accessible, combine large, publicly available correlational data with cross-sectional experimental designs and/or naturalistic experiments
   - In any design, at the absolute minimum, collect data on the type of HC being used by women in your study (specifically, progestin type and method of administration)
   - If possible, also collect data on:
   - Progestin and estradiol dosage in HC type being used
   - Duration of HC use (current method)
   - Duration of HC use (all methods), age of HC first use/onset, and why women began using HCs (overall and/or current method)
   - Mental health diagnoses and history, other medication use, and history of endocrine/hormonally-related disorders
   - Sexual activity and relationship status
   - Register your study as a clinical trial to increase its viability to clinicians and women

Note. HC = hormonal contraceptive.

5. General discussion

Most women will be on hormonal contraceptives at some point in their lives (Daniels and Jones, 2013). Unfortunately, for some women, this is experience is not a particularly pleasant one. A large proportion of women who use HCs experience psychobehavioral side effects (Sanders et al., 2001). HC use is associated with decreased libido (Both et al., 2019; Smith et al, 2014), altered stress responses (Kirschbaum et al., 1999; Kumsta et al., 2007; Lovallo et al., 2019; Merz, 2017; Nielsen et al., 2013; Rohleder et al., 2003; Roche et al., 2013), and, in at least some women using some HCs, increased rates of mood-related disorder diagnoses, (Bengtsdotter et al., 2018; Skovlund et al., 2016). Research suggests that contemporary women may be less willing to tolerate these side effects than were previous generations of women. There has been a 9% decline in use of HCs in the US in the last fifteen years (Women's Health Policy, 2019), suggesting that women are increasingly likely to

walk away from hormonal forms of contraception if it does not meet their needs.

Among the needs that is most salient to HC users and former-users is the need to minimize side effects. The majority of women who discontinue HC treatment do so because of unwanted side effects, particularly those that impact mood or other psychobehavioral states (Sanders et al., 2001). This presents an important opportunity for researchers in the areas of psychology and neuroscience, who are in a position to do the type of translational research that is needed, to understand the various factors that contribute to women's often disparate experiences on HCs. Currently, very little is known about the factors that impact individual women's oftentimes very different experiences on HCs.

In the preceding sections, we identified promising targets of inquiry for researchers seeking to better understand woman, prescription, and temporal factors that may.

contribute to women's differing experiences on HCs. In particular, we identified variables that previous research suggests may play an important role in how women metabolize, transduce, and respond to the exogenous sex hormones in their HCs. Box 4 summarizes these research targets and provides examples of research questions for researchers to consider for each. Although we took care in our use of the literature to guide our suggestions for targets of inquiry, these targets are by no means exhaustive. Our intention with this paper was to start a conversation about these moderators, but there are undoubtedly factors that we unintentionally overlooked. We urge researchers in this area to continue the conversation about factors that may contribute to the observed variability in women's experiences with HCs to provide research fodder for current and future generations of researchers doing the science necessary to understand women's.

psychobehavioral side effects when using HCs and to offer them a more personalized approach to their birth control.

After our discussion of variables that we see as offering promise as moderators of women's psychobehavioral responses to HC use, we described research approaches that can be effectively used to address these questions. Research aimed at identifying factors that moderate the range of psychobehavioral effects that women can experience on HC treatment pose some difficult challenges for researchers, including expense, large sample size needs, heterogeneity in products, and ethical considerations. Although we addressed research approaches that can help address and minimize some of these concerns (and make the results of the research more visible to clinicians), the recommended approaches are not without challenge. It can be difficult, for example, to access others' data or find appropriate corporate research partners who are willing to share data. Further, the funding landscape for researchers hoping to better understand the psychobehavioral effects of HC or to promote a precision medicine approach to HC treatment is relatively bleak. Because the clinical standards for safety and efficacy have been met for HCs, many funding agencies that support health-related research consider the issue of birth control for women to be "solved". That is, they do not recognize the need for research that explores how we can minimize the physical, psychological, and behavioral burden of HC use on women. It is our hope that increasing awareness of the need for research in this area –as is being done with this special issue – will attract the attention of policymakers who are responsible for making decisions about healthcare spending on women's health-related issues.

Despite HCs being commercially available for more than 60 years, little is known about their effects on the brain and the ways that women experience the world. Less yet is known about the factors that are responsible for women's often divergent responses to HC use. Not all women respond the same way to the same types of treatments. Understanding the factors that contribute to this variability therefore represents an important next step toward the development of a precision-medicine approach to HC treatment. Such an approach would minimize the psychological burden of contraception on women and increase the probability that they continue HC treatment, thereby minimizing their unintended pregnancy risk. It is our hope that the current work provides researchers with a spark of interest and the tools necessary to conduct this important translational work that has the potential to improve the lives of millions of reproductive-aged women.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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