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Comment on "Large-scale GWAS reveals insights into the genetic architecture of same-sex sexual behavior"

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The phenotypic measures used by Ganna *et al.* (Research Articles, 30 August 2019, p. 882) lump together predominantly heterosexual, bisexual, and homosexual individuals, including those who have experimented with a same-sex partner only once. This may have resulted in misleading associations to personality traits unrelated to understood categories of human sexuality. Scientific studies of human sexuality should use validated and reliable measures of sexual behaviors, attractions, and identities that capture the full spectrum of complexity.

Human sexuality is complex and variable, and despite its biological and social importance, its underlying developmental pathways and the sources of individual differences in sexuality are not well understood. Most scientists studying human sexuality today recognize the combined influence of multiple biological, psychological, and cultural factors in shaping sexual behaviors and identities. Genetic studies have the potential to contribute important new information by identifying specific genes and biological processes that, in combination with the environment and social dynamics, are involved in sexual expression.

The recent genetic study of same-sex sexual behavior by Ganna *et al.* (*1*) attracted wide notice on account of its large sample size and impressive genome-wide mapping coverage. However, as with all studies of complex traits, the accuracy of the phenotype is as important as sample size and genotyping methodology. Ganna *et al.*'s use of a dichotomous measure of ever/never having engaged in same-sex sexual behavior lumps together predominantly heterosexual, bisexual, and homosexual individuals—including those who experimented with a same-sex partner only once—into one composite category that is inconsistent with decades of theoretical and empirical research on sexual diversity and makes their results difficult to interpret in terms of current understanding of human sexuality. Moreover, their suggestion of rejecting standard measures of sexuality, such as the nearly 70-year-old "Kinsey scale" (which measures sexual orientation on a continuum) (*2*), on the basis of genetic correlations is an inversion of the scientific process; it should be sexological research, based on systematic observation and replication, that drives genetic and other exploratory mechanistic inquiries, not the other way around.

The primary phenotype studied by Ganna *et al.* was a self-reported measure determined with the single question "Have you ever had sexual intercourse (vaginal, oral, or anal) with someone of the same sex?" Individuals who answered No were classified as "heterosexuals" and those who answered Yes were classified as "non-heterosexuals."

This dichotomous measure was chosen by Ganna *et al.* for statistical expediency, but its use is highly problematic. The term "heterosexual" is in and of itself misleading because heterosexuality is commonly used to refer to an enduring pattern of attraction (*3*) and therefore cannot be assessed by this survey item; it would have been more accurate to use the terms "never same-sex behavior" and "ever same-sex behavior."

A key deficit of the binary measure is the heterogeneity of the resulting test group. Figure 1 shows an analysis of Ganna *et al.*'s data on the 23andMe cohort, for whom information was collected on sexual attraction, fantasy, and self-identification as well as sexual behavior. The distributions of these 7-point Kinsey-like scale measurements within the "non-heterosexual" test group are strikingly wide, including all possible categories from Kinsey 0 (other sex only) to Kinsey 6 (same-sex only). It is particularly noteworthy that more than 12% of the members of the purportedly non-heterosexual group responded that they are in fact attracted to and fantasize exclusively about individuals of the opposite sex and self-identify as exclusively heterosexual.

A second problem with the binary measure is the underlying assumption that there is a valid threshold between "heterosexual" and "non-heterosexual" that can be discerned by a single question. In support of this idea, Ganna *et al.* cite a study by Norris *et al.* (*4*) that used statistical methodology to investigate the latent structure of sexual orientation; however, even though that work combined data from three separate scales of sexual behavior, attraction, and self-identification, the "homosexual taxon" that was identified actually contained a high proportion of heterosexually identified individuals, and the methodology was unsuccessful for females. A similar study by Gangestad *et al.* (*5*) also found an appreciable overlap of individuals with heterosexual orientation in the two taxa identified by their statistical methodology.

The use of a lifetime criterion for classification is also a problematic aspect of the measure, as it is inconsistent with developmental research on sexual orientation (*6*). In particular, it groups together individuals who may have engaged in some incidental or even one-time same-sex contact, such as teenagers and emerging adults who engage in normative experimentation as sexuality develops; this is a phenotype discrete from sustained adult same-sex relationships (*7*).

The final problem is that the binary measure used by Ganna *et al.* has not been tested for reliability or validity, the hallmarks of dependable measuring tools. Indeed, there has been little if any use of such a blunt measure in the scientific literature (with the exception of some studies on sexually transmitted diseases), as it yields little information on the diversity of human sexuality. For the sake of comparison, consider a study of alcohol use based on ever/never having a single drink as the primary measure, or an analysis of child temperament based on ever/never having a tantrum.

Ganna *et al.* detected five loci that appeared to be associated with the binary measure in the main test population, three of which were replicated in additional datasets. However, none of these variants showed statistically significant elevations in participants with exclusively same-sex behavior, nor were they significantly correlated to a variable corresponding to the proportion of same-sex relative to opposite-sex partners. Thus, despite the attention paid to these genes as candidates for biological pathways of same-sex sexuality (e.g., sex hormones and olfaction), none of them were actually associated with homosexuality as that word is commonly understood.

One possible explanation for these results is that the loci identified by Ganna *at el.* have nothing to do with understood categories of human sexuality, but rather are associated with personality traits that make individuals more or less likely to seek out novel and varied experiences that include sexual experimentation. Indeed, their data show that the binary measure is genetically correlated to risk behavior and openness to experience, both of which are known to be significantly heritable (*8*, *9*).

Ganna *et al.* also used their genetic data to argue that widely used measures of sexuality, including the Kinsey scale (*2*) and the Kline sexual orientation grid (*10*), "are based on a misconception of the underlying structure of sexual orientation and may need to be rethought." It is difficult to understand how the authors arrived at this conclusion given the fundamental understanding that sexual orientation refers specifically to an enduring pattern of sexual attraction (*3*), whereas what they actually measured was lifetime behavioral occurrence with no clear indication of motivation. Furthermore, their criticism is based on a failure to find a genetic correlation between their atypical binary measure and a continuous variable of percent same-sex sexual experience, even though this may simply reflect the fact that the binary measure conflates categories/identities by including one-time experiences, behavioral bisexuality, and life-long experience. The simplest explanation of this discrepancy is that their binary measure, which is the primary phenotype in the study, has nothing to do with sexuality but rather with personality traits such as novelty seeking.

Note that although the Kinsey scale evaluates individuals' relative preference to the other sex versus the same sex on a 7-point continuum, it makes no presumptions about the structure of the underlying distribution or the underlying causes of variation; it is simply a measuring stick, developed from a taxonomic perspective (*11*). Moreover, it has been replicated in a wide variety of populations, and—at least in males—it correlates with physiological sexual response (*12*, *13*) and neural activity (*14*). Clearly, there are many aspects of sexuality that are not interrogated by this one scale and may require additional measuring tools or combinatorial scales (*15*). The key issue is whether measures are consistent and comprehensible.

The overly simplistic "ever or never" behavioral phenotype used by Ganna *et al.* led to widespread public confusion about the meaning of their study. Most accounts of the research, both in the scientific and mass media, focused on the research's implications for "gay genes," "sources of same-sex attraction," and "causes of homosexuality," even though the study did not in fact investigate attraction or sexual orientation.

Although all genetic studies of complex traits require precise and valid phenotypic measures, this is especially important for sexuality given its social, political, and personal ramifications. Future investigations on this important, complex, and dynamic aspect of human nature should leverage interdisciplinary research teams and make use of the methodological knowledge already garnered from decades of sexology research.

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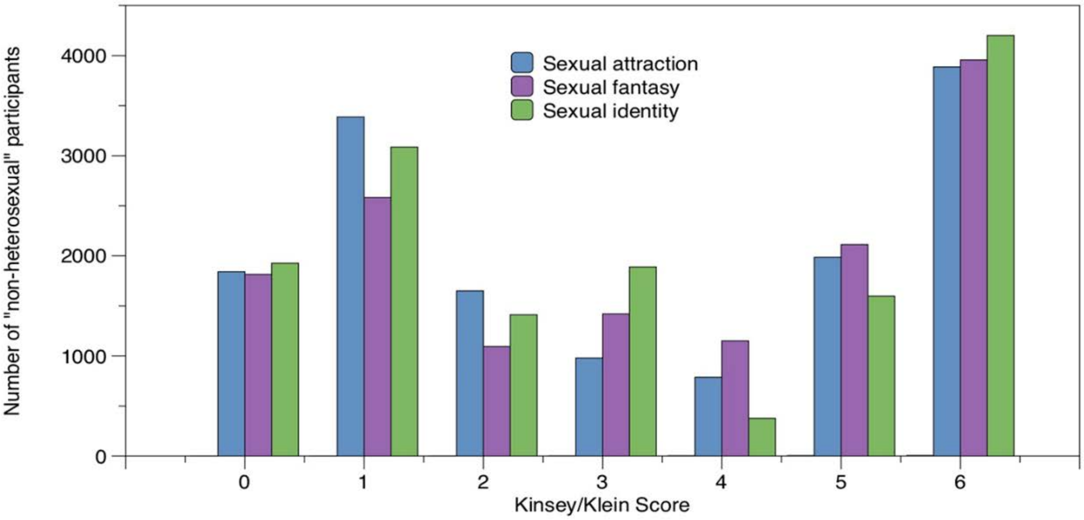

Fig. 1. Distribution of Kinsey-like scale measurements for the 23andMe "non-heterosexual" test group. Participants rated their Sexual Experience, Sexual Attraction, Sexual Fantasy, and Sexual Identity on a 7-point Likert scale ranging from "Other sex only" to "Same-sex only" for the Experience, Attraction, and Fantasy scales, and ranging from "Heterosexual only" to "Homosexual only" for the Identity scale. The Sexual Experience question was transformed into a dichotomous variable and used as the main phenotype, with participants who answered 0 (other sex only) being considered as heterosexuals and those who answered 1 (other sex mostly) to 6 (same-sex only) as non-heterosexuals. Shown are the distributions of scores on the Sexual Identity, Attraction, and Fantasy scales for the "non-heterosexual" test group used for genetic analysis by Ganna *et al*. ($n = 14{,}520$).