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Genetic Determinants of Beverage Consumption: Implications for Nutrition & Health

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Abstract

Beverages make important contributions to nutritional intake and their role in health has received much attention. This review focuses on the genetic determinants of common beverage consumption and how research in this field is contributing insight to what and how much we consume and why this genetic knowledge matters from a research and public health perspective. The earliest efforts in gene-beverage behavior mapping involved genetic linkage and candidate gene analysis but these approaches have been largely replaced by genome-wide association studies (GWAS). GWAS have identified biologically plausible loci underlying alcohol and coffee drinking behavior. No GWAS has identified variants specifically associated with consumption of tea, juice, soda, wine, beer, milk or any other common beverage. Thus far, GWAS highlight an important behavior-reward component (as opposed to taste) to beverage consumption which may serve as a potential barrier to dietary interventions. Loci identified have been used in Mendelian randomization and gene×beverage interaction analysis of disease but results have been mixed. This research is necessary as it informs the clinical relevance of SNP-beverage associations and thus genotype-based personalized nutrition, which is gaining interest in the commercial and public health sectors.

Keywords

genetics; beverage; coffee; alcohol; milk; Mendelian randomization; gene-diet interaction; beverage consumption; public health

1. INTRODUCTION

Water is an essential nutrient for life (Jéquier & Constant, 2009). Beverages contribute approximately 80% to total water intake with the remainder provided by solid foods (EFSA, 2010; Electrolytes & Water, 2005). After water, coffee, tea, beer, milk, 100% juice, sugar sweetened beverages (SSB) and wine are among the most widely consumed beverages in the world (Euromonitor, 2018; Neves, Trombin, Lopes, Kalaki, & Milan, 2012; Singh et al., 2015). Unlike plain water, beverages are also important sources of energy, other vitamins and minerals as well as 1000s of non-nutrients, many of which are bioactive. Coffee and tea, for example, are naturally energy-free but important sources of caffeine and polyphenols.

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Beer and wine both contain alcohol but also present with unique constituents including hops and resveratrol, respectively. Juice and SSB are both energy dense but the former is also a natural source of vitamins.

With their wide consumption and contributions to nutrient intake there is great interest in the role beverages play in health. Epidemiological studies support a beneficial role of moderate coffee intake in reducing risk of several chronic diseases but heavy intake is likely harmful on pregnancy outcomes (Poole et al., 2017). Tea might also reduce risk of type 2 diabetes (T2D), metabolic syndrome (MetS)(Marventano et al., 2016; Yang, J., Mao, Xu, Ma, & Zeng, 2014), osteoporosis (Sun et al., 2017) and cardiovascular diseases(CVD)(Pang et al., 2016). Wine drinking may have a dose-dependent association with health: low doses might protect against breast cancer and CVD while high doses offer no benefit or increased risk (Chen, J. Y. et al., 2016; de Gaetano, Di Castelnuovo, Rotondo, Iacoviello, & Donati, 2002). Health benefits or risks specific to beer and milk are unclear (Gijsbers et al., 2016; Guo, J. et al., 2017; Kaplan, Palmer, & Denke, 2000; Larsson, Crippa, Orsini, Wolk, & Michaelsson, 2015; Lee, J., Fu, Chung, Jang, & Lee, 2018; Li, F. et al., 2011; Liu et al., 2015; Mullie, Pizot, & Autier, 2016; Soedamah-Muthu et al., 2011). There are currently no health benefits to SSB consumption but rather convincing data supporting its role in obesity which is, in turn, a risk factor for several diseases (Malik et al., 2010; Malik, Schulze, & Hu, 2006). A caveat to our knowledge pertaining to beverage consumption and human health is that much of it is derived from epidemiological studies which have limitations (Rothman KJ, 2008; Taubes, 1995; Willett, 1998).

This review focuses on the genetic determinants of common beverage consumption and how research in this field is contributing insight to what and how much we consume and why this genetic knowledge matters from a research and public health perspective.

2. DETERMINANTS OF BEVERAGE CONSUMPTION

Understanding factors contributing to beverage consumption has important public health and research implications. Knowledge of both external and internal cues for beverage intake may inform the causal role each beverage has in health (research) and the potential population subgroups most susceptible to the health consequences of its regular consumption (public health). Thirst is an important determinant of beverage intake, but in today's society the amount and choice of beverage consumed is governed by a multitude of individual and societal factors such as availability, mood, social context, health status, education, convenience, cost, cultural influences, and sensory attributes such as smell and taste (Block, Gillman, Linakis, & Goldman, 2013; Drewnowski, 1997; Drewnowski, Henderson, Levine, & Hann, 1999; Glanz, Basil, Maibach, Goldberg, & Snyder, 1998; Neumark-Sztainer, Story, Perry, & Casey, 1999; Wardle, Carnell, & Cooke, 2005). Consumption of coffee, for example, tends to positively correlate with age, smoking, and alcohol consumption and may also be impacted by perceived health consequences of the beverage (Cornelis, M. C., 2012). Degree of economic development, religious and cultural norms, the availability and the level and effectiveness of policies are societal factors contributing to alcohol consumption behaviors while age, gender, social economic status (SES) and prior alcohol exposure are important individual level factors (Babor et al., 2010). The acute positive or negative

reinforcing properties of alcohol and caffeine are especially important in determining alcoholic beverage and coffee drinking patterns (Cornelis, M. C., 2012; Koob & Volkow, 2016; Kuntsche, Knibbe, Gmel, & Engels, 2005). Physiological effects of beverages are intrinsic and often vary between individuals. Genetics also play a role in beverage consumption behavior and more likely with regards to these physiological effects.

3. GENETIC DETERMINANTS OF BEVERAGE CONSUMPTION

Twin studies have largely been the standard approaches to estimating the genetic or heritable component of beverage consumption behaviors which can vary from 0 (not heritable) to 1 (completely inherited). Twin studies estimate heritability by comparing monozygotic twins, who share the common environment and have identical genetics, to dizygotic twins, who also share the common environment but only half their genetics (Neale & Cardon, 1994; Turkheimer, D'Onofrio, Maes, & Eaves, 2005).

In an earlier twin study by de Castro (de Castro, 1993), the heritability estimate for amount of drinking water consumed was 0.43, which was slightly higher than the 0.37 estimate for total water (food and beverages). Heritability estimates for alcohol, soda, milk, coffee and fruit juice were 0.45, 0.54, 0.04, 0.69 and 0.12, respectively. Hasselbalch et al (Hasselbalch, Ann Louise, 2010) reported lower estimates for soda: 0.26 and 0.30 for men and women, respectively, while Teucher et al (Teucher et al., 2007) reported a much higher estimate for fruit juice (0.70). Heritability estimates for self-reported total caffeine intake (derived from caffeine-containing coffee, tea and soda) ranged between 0.30 and 0.58, with higher estimates reported for heavy use (up to 0.77)(Yang, A., Palmer, & de Wit, 2010). Studies that separated heritability estimates by caffeine source report higher heritability for coffee relative to other sources (Luciano, Kirk, Heath, & Martin, 2005; Teucher et al., 2007; Vink, Staphorsius, & Boomsma, 2009). Twin studies as well as family and adoption studies of habitual alcohol consumption or alcoholism have largely focused on males and report heritability estimates between 0.30 and 0.60 (Carol A. Prescott & Kenneth S. Kendler, 1999; McGue, Matt, 1999; Reed et al., 1994; Teucher et al., 2007). Heath and Martin (Heath, A. & Martin, 1988) propose that the decision to abstain from drinking is not genetically determined, but the onset and amount consumed once that decision is made are influenced by genetic factors.

Twins studies are powerful epidemiological approaches to measuring the contribution of genetics to a given trait but are often underpowered and subject to bias which likely add to between study differences in estimates of heritability (Kendler, 1993; Zaitlen & Kraft, 2013; Zuk, Hechter, Sunyaev, & Lander, 2012). Furthermore, although results above provide compelling evidence for a genetic influence on beverage intake and choice, they do not indicate the specific genes that increase or decrease drinking behaviors.

3.1. Early Approaches: Linkage and Candidate Gene Analysis

The earliest efforts in gene-trait mapping involved genetic linkage and candidate gene analysis. Genetic linkage studies determine inheritance of a binary or quantitative trait among family members in extensive pedigrees by evaluating whether one or more genetic markers spaced across the 23 chromosomes segregate with the trait (Cantor, 2014).This

approach roughly locates a broad chromosomal region, which may contain 10s of 100s of genes, that co-segregate with the trait. Other strategies such as fine mapping and targeted association analysis must be used to further refine the linked region and identify the gene of interest (Cantor, 2014).

Lactose intolerance (or lactase non-persistence) is a common autosomal recessive condition resulting from the physiological decline in activity of lactase-phlorizin hydrolase (LPH) in intestinal cells after weaning and has a significant impact on milk drinking behavior. The age of onset varies between populations and in some populations lactase activity persists at a high level throughout adult life (Sahi, Timo, 1994; Sahi, T, Isokoski, Jussila, & Launiala, 1972; Swallow, 2003; Wang, Y. et al., 1998). Although the sequence of the lactase gene (*LCT*, encoding LPH) had been known since 1991 (Boll, Wagner, & Mantei, 1991), the causative mechanism for lactase persistence remained elusive until 2002 when a linkage analysis of nine Finnish families with hypolactasia identified a variant upstream of the initiation codon of *LCT* (LCT-13910C>T) which demonstrated complete association with lactase persistence (Enattah et al., 2002).

The first linkage studies on alcohol dependence (AD) from the family-based Collaborative Study on the Genetics of Alcoholism (COGA) (Reich et al., 1998) and a sib-pair study from a Southwest American Indian tribe (Long et al., 1998) reported a broad risk locus on chromosome 4q that contains the genes that encode the isoforms of alcohol dehydrogenase (ADH). Hill et al (Hill et al., 2004) reported support for AD loci at chromosome 1q23.3-q25.1 in a genome-wide linkage analysis of double probands. This region was followed up using fine-mapping genotyping and confirmed single nucleotide polymorphism (SNP)-AD associations within *ASTN1* (Hill, Weeks, Jones, Zezza, & Stiffler, 2012). Additional AD studies have implicated other chromosomal regions (Dick et al., 2010; Edenberg, Howard J & Foroud, 2014; Wang, Jen C et al., 2004). The genetic linkage approach, to the author's knowledge, has not been applied to *habitual* beverage consumption.

A second approach to isolating genetic determinants of a trait involves genetic association in population or family base-studies and is essentially a form of linkage mapping but is allele-based rather than locus-based and is often hypothesis driven. Efforts focus on potentially functional SNPs in genes with biological plausibility or in regions identified by linkage. In the context of beverage consumption behavior a highly implicated pathway pertains to taste. Taste is one of the primary means of determining the acceptability of a food and might have been critical to the survival of early human subjects (Tepper, 2008). The perception of sweet, umami and bitter tastes are all mediated via G-coupled protein receptors, encoded by the *TAS1R* and *TAS2R* taste receptor gene families, while salty and sour tastes are transduced via ion channels (Wise, Hansen, Reed, & Breslin, 2007). There is little known regarding genetic variation in salty and sour tastes(Wise et al., 2007). In contrast, bitter taste quality is affected by variants in *TAS2R16, TAS2R38, TAS2R43* and *TAS2R44* while variants in *TAS1R1* and *TAS1R3* impact umami and sweet (Drayna, 2005; Feeney, O'Brien, Scannell, Markey, & Gibney, 2011; Kim, U. K. et al., 2003; Mainland & Matsunami, 2009; Shigemura, Shirosaki, Sanematsu, Yoshida, & Ninomiya, 2009). The most studied is *TAS2R38*, in particular its three SNPs, which result in two common haplotypes that are named for their amino acid substitutions: PAV (proline, alanine, and valine) and AVI

(alanine, valine, and isoleucine) (Kim, U.-K., Breslin, Reed, & Drayna, 2004). *TAS2R38* diplotype influences the ability to taste a family of bitter compounds including phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP). Although these compounds are not found in food stuffs naturally, PTC/PROP-related compounds are present in several bitter tasting fruits and vegetables. PAV homozygotes and heterozygotes perceive greater bitterness than AVI homozygotes that perceive little or no bitterness (Kim, U.-K. et al., 2004). This locus has been subject to numerous association studies of food and beverage preferences. Variation in *TAS2R38* has been linked to coffee, beer, spirits, green tea, sugar content of beverages and total alcohol or drinking status (Beckett et al., 2017; Choi, J. H., Lee, Yang, & Kim, 2017; Duffy et al., 2004; Hayes et al., 2011; Mennella, Pepino, & Reed, 2005; Ong et al., 2018; Ooi, Lee, Law, & Say, 2010; Perna et al., 2018; Ramos-Lopez, O. et al., 2015; Wang, J. C. et al., 2007). Variation in other *TAS2R* members have also been linked to bitter beverage consumption (Cornelis, M. C., 2012; Hayes et al., 2011; Ong et al., 2018; Pirastu et al., 2014; Wang, J. C. et al., 2007). Most of these findings, however, lack replication. Although bitterness is widely claimed to be an evolutionarily important indicator of toxicity (Behrens & Meyerhof, 2016; Drewnowski & Gomez-Carneros, 2000) not all bitter stimuli are toxic (Glendinning, 1994; Nissim, Dagan-Wiener, & Niv, 2017). Coffee and beer are prime examples whereby the innate eversion to bitter taste does not hold. Indeed, variants in *TAS2R43* linked to increased perception of caffeine; a bitter compound, associates with increased coffee consumption and liking according to candidate-SNP analysis (Ong et al., 2018; Pirastu et al., 2014). Although coffee bitterness is easily offset by additives, some individuals may also learn to associate this sensory cue with social context or postingestive signals elicited by biologically active constituents of coffee. Variation in the *TAS1R* sweet and umami receptor family has also been linked to alcohol consumption behavior (Choi, J. H. et al., 2017), wine drinking (Choi, J. H. et al., 2017) and vodka liking (Pirastu et al., 2012).

Besides taste-related genes, the candidate approach for alcohol-related traits has additionally focused on alcohol metabolism genes including *ADH, CYP2E1* and *ALDH* (Figure 1), as well as gene members of several neurotransmitter systems: *GIRK1, GABA-A, DRD2, SLC6A3, SLC6A4, TPH1, COMT, CHRM2* and *OPRM1*(Edenberg, H. J. & Foroud, 2006; Matsuo et al., 2006; Reilly, Noronha, Goldman, & Koob, 2017; Tawa, Hall, & Lohoff, 2016). For coffee and tea drinking, candidate genes involved in caffeine metabolism (*CYP1A2*) and caffeine's target of action (*ADORA2A, DRD2*) have been examined (Cornelis, M. C., 2012; Cornelis, M. C., El-Sohemy, & Campos, 2007). Gene members of the brain reward system, particularly *DRD2*, have been tested for associations with SSB (Baik, J.-H., 2013; Eny, Corey, & El-Sohemy, 2009; Ramos-Lopez, Omar, Panduro, Rivera-Iñiguez, & Roman, 2018).

3.2. Recent Approaches: Genome-wide analysis

With the human genome sequenced in the early 2000's and mapped frequencies and patterns of association among millions of common SNPs in diverse populations, the primary approach to identifying genetic variants for complex traits has quickly transitioned to genome-wide association studies (GWAS). GWAS is based on the premise that a causal variant is located on a haplotype, and therefore a marker allele in linkage disequilibrium

(LD) with the causal variant should present with an association with a trait of interest (Hirschhorn & Daly, 2005). This approach is unbiased with respect to genomic structure and previous knowledge of the trait etiology, which contrasts with earlier approaches, and therefore has greater potential to reveal novel gene-trait associations.

Table 1 provides descriptions of GWAS listed in the GWAS catalogue (November 26, 2018) reporting significant SNP-drinking behavior associations. GWAS designs included single sample, 2-stage (i.e. discovery and replication) and meta-analysis. Table 2 presents those loci defined as significant according to authors' a priori threshold. Results of GWAS of AD and beverage 'liking' were also included.

Alcohol—Successful GWAS of alcohol-related traits have been undertaken in European, African American, Asian and Hispanic Latino populations. Most of these targeted AD and included study samples with a high proportion of individuals with comorbid psychiatric disorders and/or co-occurring drug dependence. Several efforts report null findings (Heath, A. C. et al., 2011; Kapoor, M. et al., 2014; Lydall et al., 2011; Mbarek et al., 2015; McGue, M. et al., 2013; Zuo, L. et al., 2012), but inability to replicate some loci may be a function of both case and control ascertainment (Frank et al., 2012; Mailman et al., 2007). Most robust are associations with potentially functional SNPs that alter alcohol metabolism (Fig.1). For example, the *ADH1B* rs1229984 T allele (48His) results in a 40 to 100-fold higher rate of alcohol to acetaldehyde metabolism (i.e ethanol oxidation)(Edenberg, Howard J, 2000; Hurley, Bosron, Stone, & Amzel, 1994). The *ALDH2* rs671 A allele (504Lys) reduces *ALDH2* activity and thus decreases acetaldehyde to acetate metabolism (i.e. acetaldehyde oxidation)(Bosron & Li, 1986; Enomoto, Takase, Yasuhara, & Takada, 1991; Harada, Misawa, Agarwal, & Goedde, 1980; Quillen, Ellen E. et al., 2014). Acetaldehyde is a toxic substance whose accumulation leads to a highly aversive reaction that includes facial flushing, nausea, and tachycardia. The *ADH1B* His and *ALDH2* Lys variants influence alcohol drinking behavior by elevating blood acetaldehyde levels upon alcohol drinking which ultimately reduces susceptibility to developing alcohol drinking problems (Macgregor et al., 2009; Peng, Y. et al., 2010; Takeuchi et al., 2011; Yokoyama et al., 2008).

ALDH2 and *ADH1B* are the only susceptibility genes that were studied as candidate SNPs before they were highlighted via agnostic GWAS (Li, D., Zhao, & Gelernter, 2011; Takeuchi et al., 2011). Variants in *SERINC2, KIAA0040, MTIF2-CCDC88A*, and *PECR* have also been associated with AD in GWAS. Variation in *SERINC2*, encoding a transmembrane transporter of L-serine, may potentially alter glycine and glutamate neurotransmission contributing to hyperexcitability and negative affect during alcohol abstinence (Furuya & Watanabe, 2003; Hirabayashi & Furuya, 2008; Reilly et al., 2017; Smith, Q. R., 2000; Tabatabaie, Klomp, Berger, & De Koning, 2010). *KIAA0040* has no obvious role in alcohol consumption behavior but is closely situated to i) *ASTN1*, which has been associated with AD and substance dependence (Gratacòs et al., 2009; Hill et al., 2012), ii) *TNN* encoding tenascin-N; involved in neurite outgrowth and cell migration in hippocampal explants and iii) *TNR*, encoding tenascin-R; an extracellular matrix protein expressed primarily in the central nervous system and has been related to multiple brain diseases (Reilly et al., 2017). *CCDC88A* is the most promising candidate at 2p16, a region also implicated in a previous linkage study of AD (Dick et al., 2010). *CCDC88A* is differentially expressed in AD

(Gelernter, J. et al., 2013) and interacts with *DISC1*, a gene associated with both schizophrenia (Kim, J. Y. et al., 2012) and opioid dependence (Xie et al., 2014). *PECR* encodes a protein that participates in chain elongation of fatty acids and is an integral component of peroxisomes which play a key role in protection against oxidative stress particularly in glial cells (Di Cesare Mannelli, Zanardelli, Micheli, & Ghelardini, 2014; Varga, Czimmerer, & Nagy, 2011). Variants at 5q35, 6p21, and 7q32 have also been associated with AD symptoms but not clinically diagnosed AD.

Variants linked to AD may not necessarily equate with habitual alcohol consumption in general population. The latter has been addressed by independent GWAS often involving several 1000s of individuals. Indeed, aside from *ALDH2* and *ADH1B*, none of the loci associated with habitual alcohol consumption associate with AD, although this may be a function of the study design rather than real biological differences between these traits. Variants in *CADM2* associated with alcohol consumption have also been associated with cognitive ability, reproductive success, risk-taking propensity and cannabis use (Davies, G. et al., 2016; Day et al., 2016; Ibrahim-Verbaas et al., 2016; Stringer et al., 2017). Following-up on their well replicated *KLB*-alcohol association (Clarke et al., 2017; Jorgenson et al., 2017; Schumann, Gunter et al., 2016), Schuman et al (Schumann, Gunter et al., 2016) identified a liver-brain axis linking the liver hormone FGF21 with central regulation of alcohol intake involving β-Klotho receptor (encoded by *KLB*) in the brain. FGF21 is induced in liver and released into the blood in response to various metabolic stresses, including high-carbohydrate diets and alcohol (Dushay et al., 2015; Sanchez, Palou, & Pico, 2009; Zhao, C. et al., 2015). FGF21 was also shown to suppress sweet and alcohol preference in mice (Talukdar et al., 2016; von Holstein-Rathlou et al., 2016). The function of another GWAS AD candidate, *AUTS2*, is unknown, but significant differences in expression of *AUTS2* in whole-brain extracts of mice selected for differences in voluntary alcohol consumption as well as reduced alcohol sensitivity in Drosophila with a downregulated *AUTS2* homolog (Schumann, G. et al., 2011) support a potential role of *AUTS2* in alcohol drinking behavior. The role of other loci associated with alcohol-related traits is unclear and/or require stronger support in independent studies.

Coffee—GWAS have identified multiple genetic variants associated with self-reported habitual coffee consumption (Amin et al., 2012; Coffee and Caffeine Genetics Consortium et al., 2015; Cornelis, M. C. et al., 2011; Sulem et al., 2011; Zhong et al., 2018), many of which point to caffeine-related pathways. All of these GWAS have been population-based but predominately of individuals of European Ancestry. The earlier GWAS confirmed loci near *AHR, CYP1A2, POR*, and *ABCG2* which generally present with the largest effect sizes and likely impact drinking behavior indirectly by altering the metabolism of caffeine and thus the physiological levels of this compound available for its psychostimulant effects. CYP1A2, for example, is responsible for over 95% of caffeine metabolism (Thorn, Aklillu, Klein, & Altman, 2012). Indeed, a subsequent GWAS of circulating caffeine metabolite levels further informed the roles of these loci in caffeine metabolism (Cornelis, M. C. et al., 2016). Genetic variants leading to increased coffee/caffeine consumption associate with lower circulating caffeine levels and higher paraxanthine-to-caffeine ratio suggesting a fast caffeine metabolism phenotype (Cornelis, M. C. et al., 2016). Loci near *ADORA2A, BDNF*

and *SLC6A4* likely act directly on coffee drinking *behavior* by modulating the acute psychostimulant and rewarding properties of caffeine. GWAS and smaller follow-up studies have linked several of these loci to consumption of regular coffee, decaffeinated coffee, tea, total caffeine and water and further extended the findings to African American and Japanese populations (Coffee and Caffeine Genetics Consortium et al., 2015; McMahon, Taylor, Smith, & Munafo, 2014; Nakagawa-Senda et al., 2018; Taylor, Davey Smith, & Munafò, 2018). Only one locus is implicated in the sensory properties of coffee (*OR8U8)* and was discovered when GWAS sample sizes exceeded 300, 000 (Zhong et al., 2018). Variants near *MLXIPL, GCKR, SEC16B, TMEM18, AKAP6* and *MC4R* have no obvious role in coffee or caffeine consumption but have previously been associated with other traits in GWAS notably obesity, glucose and lipids (Table 2)(MacArthur et al., 2017). A recent GWAS among Japanese reported an association between coffee consumption and the *ALDH2* locus which persisted upon adjustment for alcohol intake, BMI and smoking and in stratified analysis based on alcohol drinking status (Nakagawa-Senda et al., 2018). Pirastu et al has performed GWAS of coffee intake (Pirastu, Kooyman, Robino, et al., 2016) and coffee liking (Pirastu, Kooyman, Traglia, et al., 2016) and identified associations with variants in *PDSS2* and *FIBIN*, respectively. A role of proteins encoded by these genes in coffee intake or liking is unclear.

Bitter and Sweet Tasting Beverages—We recently conducted a GWAS of habitual bitter and sweet beverage consumption based on the premise that taste perceptions and preferences are heritable and determinants of beverage choice and intake (Zhong et al., 2018). Phenotypes consisted of groups of beverages characterized by similar taste (Table 1) as defined in earlier work (Cornelis, M. C., Tordoff, El-Sohemy, & van Dam, 2017). All loci associated with total bitter beverage consumption were previously associated with coffee intake in earlier GWAS (Table 2). Sub-phenotype analyses targeting the alcohol and caffeine components of beverages yielded additional loci and were discussed above with alcohol and coffee loci.

No locus was replicated for total sweet beverage consumption, but a GWAS of SSB yielded significant variants mapping to *FTO*, a well-established locus for BMI and obesity-related traits(MacArthur et al., 2017). We found that variants in *FTO* previously linked to higher BMI were associated with lower SSB consumption regardless of BMI adjustment and is consistent with a previous candidate gene study by Brunkwall et al (Brunkwall et al., 2013).

In summary, GWAS have discovered plausible as well as novel loci underlying alcohol and coffee drinking behavior. Many of these loci affect drinking behavior by modulating the physiological levels of bioactive constituents (i.e. acetaldehyde, caffeine). To our knowledge, no GWAS has identified variants specifically associated with consumption of tea, juice, milk or any other beverage intake. Differential success might be a function of heritability, SNP effect size, precision in drinking behavior measurement or other factors impeding power for detection.

Beverage-related loci mapping to *GCKR, MLXIPL, FTO, MC4R, SEC16B*, and *TMEM18* are interesting since they are also GWAS loci for metabolic traits (Table 2). *GCKR* encodes the glucokinase regulatory protein that is produced by hepatocytes and is responsible for

phosphorylation of glucose in the liver; a property that aligns more with metabolic traits than behavioral traits. *FTO*, *MC4R, SEC16B,* and *TMEM18* are all obesity loci. The genetic variant in *FTO* that increases risk for obesity has also been associated with increased alcohol, coffee and sweet food consumption but lower consumption of soft drinks and SSB according to independent candidate SNP analysis (Brunkwall et al., 2013; Sobczyk-Kopciol et al., 2011; Zhong et al., 2018), adjusted for BMI. These findings might suggest that the effect of *FTO* on beverage choice might depend on the form (liquid versus solid) and energy density (high-caloric versus low-caloric), independent from *FTO*'s effect on BMI. Neverthless, increasing evidence suggests that a subset of BMI loci contribute to behavioral aspects of obesity by altering food and beverage intake (Brunkwall et al., 2013; Hasselbalch, Ann L et al., 2010; Loos & Yeo, 2014; Sobczyk-Kopciol et al., 2011; Willer et al., 2009).

GWAS of beverage drinking behavior highlight an important behavior-reward component to beverage choice and thus adds to understanding the link between genetics and beverage consumption and the potential barriers to dietary interventions. Interestingly, GWAS do not suggest a major role of variation in taste on drinking behaviors; a direction taken in prior candidate gene analysis.

4. IMPLICATIONS OF GENETIC KNOWLEDGE ON BEVERAGE CONSUMPTION

4.1. Research Tools

An immediate application of the loci identified via GWAS has been for optimizing epidemiological research on beverages and health. Nutritional epidemiology is often criticized for lack of reliable progress (Archer, Lavie, & Hill, 2018; Ioannidis, 2018; Trepanowski & Ioannidis, 2018). Difficulty detecting small effect sizes, accounting for confounding, measuring diet and suboptimal research reporting are amongst the problems with the field (Trepanowski & Ioannidis, 2018). Randomized control trials (RCTs) may address these problems but also bare limitations (Trepanowski & Ioannidis, 2018). Integrating genetic information by way of Mendelian randomization (MR) and gene- or SNP-diet interaction (G×D) analysis offers an efficient alternate solution to issues faced by traditional nutritional epidemiology. Because alleles segregate randomly from parents to offspring, offspring genotypes are unlikely to be associated with confounders in the population. Germ-line genotypes are fixed at conception, avoiding issues of reverse causation (Zheng et al., 2017). Moreover, the biological functions of the genes of interest might also provide insight to mechanisms linking a beverage to a disease. These genetic epidemiological approaches are not new but have garnered more attention in light of new and robust GWAS findings and the availability of large genetic data sets. While earlier applications have modeled single SNPs, more recent applications have, when possible, modeled several SNPs together as a "genetic score" (GS) to boost power while also addressing model assumption violations.

MR is a technique that uses genetic variants as instrumental variables (IVs) to assess whether an observational association between a risk factor and an outcome aligns with a causal effect. If a genetic variant alters the level of an exposure of interest, then this genetic

variant should also be associated with disease risk and to the extent predicted by the effect of the genetic variant on the exposure (Davey Smith & Ebrahim, 2003; Katan, 1986). MR is a valid approach given the following assumptions are met: (1) the genetic variant is associated with the modifiable exposure of interest, (2) the genetic variant is not associated with confounders of the exposure to outcome association and (3) the genetic variant only influences the outcome through the exposure of interest (Davey Smith & Hemani, 2014). Study designs, statistical approaches and limitations of MR studies more generally have been reviewed in detail elsewhere (Davies, N. M., Holmes, & Smith, 2018; Glymour, Tchetgen, & Robins, 2012; Holmes, Michael V, Ala-Korpela, & Smith, 2017; Munafò, Tilling, Taylor, Evans, & Davey Smith, 2017; Paternoster, Tilling, & Smith, 2017; Zheng et al., 2017). Trait heterogeneity and pleiotropy are particular limitations concerning MRs of beverage consumption. A GS encompassing all beverage-trait SNPs will yield an IV reflecting multiple aspects of drinking behavior (Table 2). For coffee and alcohol, this may include caffeine or alcohol metabolism, reward-response and others. Such heterogeneity limits the ability to infer causality for particular dimensions of a beverage (e.g., alcohol vs non-alcohol) and makes interpretation of MR analyses more difficult (Holmes, Michael V et al., 2017; Zheng et al., 2017). Biological pleiotropy occurs when a genetic variant is associated with multiple exposures or traits and is therefore a violation of MR assumption 3 (Burgess & Thompson, 2015; Davey Smith & Hemani, 2014). Many loci associated with beverage drinking traits are more strongly associated with other traits based on GWAS (Table 2)(MacArthur et al., 2017). Whether this results from pleiotropy or a true causal relationship between a beverage and these other traits is unclear.

The term ‘interaction’ has various meanings but the focus of the current discussion is on G×D interaction, here defined as a joint effect of one or more genes with one or more dietary factors that cannot be readily explained by their separate marginal effects. By convention, a multiplicative model is taken as the null hypothesis: the relative risk of disease in individuals with both the genetic and dietary risk factors is the product of the relative risks of each separately. Therefore, any joint effect that differs from this prediction is considered to be a form of interaction (Rothman & Greenland, 1998; Thomas, 2010). The nature of the interaction can also vary. The main effect of both genotype and beverage intake may be greater in one stratum (i.e. intake level or genotype) than in the other strata, or it may have the opposite effect in one stratum compared with the others (Rothman & Greenland, 1998). Because some statistical techniques used in MR and G×D interactions are common it is sometimes difficult to distinguish between the approaches. While the primary goal of MR is to establish causality a unique feature of G×D interactions is they can potentially provide mechanistic insight into diet’s role in disease. Following are examples of how these methods have been applied to beverage and health research.

Alcohol—Most of the genetic epidemiological studies of alcohol have focused on the *ALDH2* Glu504Lys (rs671) and *ADH1B1* Arg48His (rs1229984) polymorphisms, wherein the *ALDH2* Lys (A allele) and *ADH1B1* His (T allele) variants associate with lower alcohol consumption due to adverse reaction to alcohol as a result of higher circulating acetaldehyde. These variants are most common in Asians (Table 2) and thus most genetic studies have included Asian populations. Several studies report that individuals with ALDH2

Lys/Lys genotype have no or a lower risk of esophageal cancer while those with Lys/Glu are at increased risk compared to Glu/Glu. This provides strong evidence that alcohol intake increases the risk of esophageal cancer and individuals whose genotype results in markedly lower intake (i.e. Lys/Lys) due to an adverse reaction to alcohol are thus protected (Fang et al., 2011; Lewis & Smith, 2005; Yang, S. J. et al., 2010; Zhang, G. H., Mai, R. Q., & Huang, B., 2010; Zhao, T. et al., 2015). Heterozygotes have a limited ability to metabolize acetaldehyde, but exhibit a less severe reaction than seen among Lys/Lys homozygotes, which enables them to drink considerable amounts of alcohol. An increased risk for this subgroup also suggests that alcohol increases risk through the carcinogenic action of acetaldehyde (Boccia et al., 2009). This is further supported by reports of *ALDH2*-alcohol interactions whereby both Lys/Lys and Lys/Glu are at increased risk of esophageal cancer when they also consume alcohol (Tanaka et al., 2010; Yang, S. J. et al., 2010; Zhang, G. H. et al., 2010). MRs and ALDH2×alcohol interaction analysis also support a causal role of alcohol intake (via acetaldehyde) in the development of gastric and head/neck cancers(Boccia et al., 2009; Hidaka et al., 2015; Matsuo et al., 2013; Shin et al., 2011; Wang, H. L., Zhou, Liu, & Zhang, 2014; Yang, S. et al., 2017). The genetic model of analysis (i.e. genotype-specific vs additive, dominant or recessive models) and the need to further account for drinking behavior appears important with regards to *ALDH2* Glu504Lys and disregard for these may explain, in part, the inconsistent results in the literature pertaining to *ALDH2* and other outcomes (Chen, B. et al., 2015; Choi, J. Y. et al., 2003; Guo, X.-F. et al., 2013; Kawase et al., 2009; Masaoka et al., 2016). *ALDH2* Lys/Lys and Lys/Glu decreased risk of ovarian cancer vs Glu/Glu in a pooled analysis of Asians (Ugai et al., 2018) supporting a causal relationship between high alcohol intake and cancer risk. However, the association was independent of alcohol intake suggesting a potential violation of MR assumption 3 (or pleiotropy) or measurement error of alcohol.

Different findings arise for *ALDH2*, alcohol and cardiometabolic traits. The *ALDH2* Lys/Lys or Lys/Glu genotypes *increased* risk of T2D compared to the Glu/Glu genotype (Li, G.-y. et al., 2017). *ALDH2* Lys *carriers* have an increased risk of CHD, CAD and MI (Gu & Li, 2014; Han et al., 2013; Wang, Q. et al., 2013; Zhang, Wang, Fu, Zhao, & Kui, 2015) and present with an at-risk lipid profile (Cho et al., 2015; Sasakabe et al., 2018; Tabara et al., 2016). Although alcohol consumption was not assessed, by traditional MR interpretations this would suggest alcohol drinking is protective for these outcomes. *ALDH2* also detoxifies reactive aldehydes, such as methylglyoxal and 4-hydroxynonenal, which derive from lipids and glucose and contribute to the formation of advanced glycation end products (Chen, C.-H. et al., 2008; Morita et al., 2013; Siraki & Shangari, 2005), implicated in T2D (Li, G.-y. et al., 2017). The formation of acetaldehyde adducts with apolipoprotein B may reduce the conversion of very low-density lipoprotein cholesterol to LDL cholesterol, which would decrease the serum LDL cholesterol level (Kesaniemi, Kervinen, & Miettinen, 1987; Savolainen, Baraona, & Lieber, 1987; Wehr, Rodo, Lieber, & Baraona, 1993). Inconsistencies in this area nevertheless arise whereby the Lys variant contributes to a lower risk of T2D (particularly in drinkers) (Peng, M. et al., 2018) and HTN(Chen, L., Smith, Harbord, & Lewis, 2008; Zhang, S. Y. et al., 2015).

For *ADH1B1* Arg48His (rs1229984), each additional Arg variant (high alcohol consumer, slow acetaldehyde producer) increased risk of esophageal and other upper aerodigestive tract

cancers (UADT) compared to His/His (Guo, H., Zhang, & Mai, 2012; Tanaka et al., 2010; Yang, S. J. et al., 2010; Zhang, G., Mai, R., & Huang, B., 2010; Zhang, G. H. et al., 2010). An interaction with alcohol drinking is also evident with risk being restricted to or even greater among drinkers with Arg/Arg or Arg/His genotypes (Guo, H. et al., 2012; Tanaka et al., 2010; Yang, S. J. et al., 2010; Zhang, G. et al., 2010; Zhang, G. H. et al., 2010). Taken together this suggests alcohol drinking and exposure to ethanol (not acetaldehyde) increases UADT cancer risk which differs slightly from results concerning *ALDH2* and cancers. In a meta-analysis including individuals of European ethnicity, individuals with an *ADH1B* His variant presented with lower measures of adiposity, blood pressure and inflammation as well as a *reduced risk* of CHD than those with Arg/Arg; and most of these associations were null in non-drinkers. This suggests that reduction of alcohol consumption, even for light to moderate drinkers, is beneficial for cardiovascular health and is contrary to the J-shaped epidemiological associations between alcohol and CVD risk previously described (Holmes, M. V. et al., 2014; Toma, Pare, & Leong, 2017).

Three recent MRs of alcohol and lupus (Bae & Lee, 2018b), RA (Bae & Lee, 2018a) and BMD (Guo, R., Wu, & Fu, 2018) used 6 to 24 independent loci identified exclusively by Clark et al (Clarke et al., 2017) (Table 1) and provided no support for a causal role of alcohol intake in these outcomes. However, only variants near *GCKR* and *KLB* were among the selected loci that have been confirmed by others (Table 2) and several IV SNPs violate MR assumptions and are thus invalid.

Coffee—Cornelis and Munafo (Cornelis, Marilyn & Munafo, 2018) recently reviewed MR studies of coffee and caffeine consumption. To date, at least fifteen MR studies have investigated the causal role of coffee or caffeine use on risk of T2D, CVD, Alzheimer's disease, Parkinson's disease, gout, osteoarthritis, cancers, sleep disturbances and other substance use. The vast majority of study IVs included at least SNPs near *CYP1A2* and *AHR* – the strongest and most robust variants linked to coffee drinking behavior (Table 2) and caffeine metabolite levels(Cornelis, M. C. et al., 2016). Single studies investigated and provided support for a causal role of coffee in reducing risk of gout (Poole et al., 2017) and increasing risk of osteoarthritis (Lee, Y. H., 2018). Four studies examined the co-occurrence of caffeine use and other substances with conflicting results (Bjørngaard et al., 2017; Treur et al., 2017; Verweij et al., 2013; Ware et al., 2017). For the remaining outcomes, studies did not provide clear support for a causal role of coffee or caffeine, but often acknowledged limitations (such as low statistical power, pleiotropy and collider bias), such that a causal role cannot yet be ruled out. In a 2014 review, over 30 gene–coffee interaction studies had been published(Cornelis, MC, 2014). Most have targeted the caffeine component of coffee but have examined a limited number of SNPs. Studies of cancers, CVD, Parkinson's disease, and pregnancy outcomes were promising but rather preliminary. Studies suggest that the caffeine component of coffee may have adverse cardiovascular effects, but that these effects are limited to individuals with the genotype corresponding to impaired or slower caffeine metabolism (Cornelis, MC, 2014). Since 2014, additional studies have been published. For example, in a large UK study, coffee of any type was associated with lower risk of mortality regardless of genetic variation in caffeine metabolism (based on *CYP1A2, AHR, POR* and *CYP2A6* (Table 2 variants)) (Loftfield et al., 2018). Casiglia et al (Casiglia et al., 2018)

reported an inverse relationship between caffeine intake and incident atrial fibrillation and this was not modified by *CYP1A2* variation. The same group reported better reasoning measures with higher caffeine intake, but this was apparent only among those with a *CYP1A2* genotype corresponding to slow caffeine metabolism (Casiglia et al., 2017). Sasaki et al (Sasaki, Limpar, Sata, Kobayashi, & Kishi, 2017) reported an inverse association between maternal caffeine consumption and infant birth size only among mothers with the *CYP1A2* genotype corresponding to rapid caffeine metabolism.

Milk—All MR studies of milk used the *LCT*-13910 C/T SNP as an IV for milk/dairy intake. Studies examined the causal role of milk/dairy in bone health, mortality, CVD and related traits, T2D, obesity and mortality (Bergholdt, H. K., Nordestgaard, & Ellervik, 2015; Bergholdt, H. K., Nordestgaard, Varbo, & Ellervik, 2015; Bergholdt, H. K. M., Larsen, Varbo, Nordestgaard, & Ellervik, 2018; Bergholdt, H. K. M., Nordestgaard, Varbo, & Ellervik, 2018; Hartwig, Horta, Smith, de Mola, & Victora, 2016; Lamri et al., 2013; Manco, Dias, Muc, & Padez, 2016; Smith, C. E. et al., 2016; Tognon et al., 2017; Yang, Q. et al., 2017). Results were null or inconsistent with the exception that the lactate persistant T allele (proxy for increased milk intake) may promote obesity (Manco et al., 2016; Yang, Q. et al., 2017).

4.2. Public Health

Personalized nutrition (PN) involves tailored dietary advice that can be delivered to individuals based on their diet and lifestyle factors. PN contrasts with the public health model which provides non-specific healthy eating advice. Since the completion of the human genome sequence, many direct-to-consumer (DTC) genetic testing services have been established and several target individuals who seek genetic–based PN (Bloss, Madlensky, Schork, & Topol, 2011; Guasch-Ferré, Dashti, & Merino, 2018). Whether genotype-based PN is scientifically sound, motivates behavior change beyond that provided by general advice or, rather, promotes a fatalistic attitude and decreased self-efficacy are just a few of the many questions being asked concerning genotype-based PN (Bouwman & te Molder, 2008; Guasch-Ferré et al., 2018).

In their recent review, O'Donovan et al (O'Donovan, Walsh, Gibney, Brennan, & Gibney, 2017) reported little evidence for the benefit of genotype-based PN on motivating behavior change. Test price and perceived seriousness of the disease were factors potentially impacting DTC testing on behavior. Horne et al (Horne, Madill, O'Connor, Shelley, & Gilliland, 2018) also reviewed research pertaining to lifestyle behavior change (nutrition, physical activity, sleep, and smoking) resulting from genetic testing interventions. The provision of actionable recommendations informed by genetic testing was more likely to facilitate behavior change than the provision of genetic information without actionable lifestyle recommendations. Several studies of good quality demonstrated changes in lifestyle habits, nutrition especially, arising from the provision of genetic interventions. More recently, the Food4Me proof-of-principle study set out to investigate the effect of varying levels of PN advice on health outcomes in comparison with general healthy eating advice (O'Donovan et al., 2017). PN advice resulted in greater dietary changes compared with general healthy eating advice, but no additional benefit was observed for PN advice based

dietary intake, phenotype and genotype information than PN advise based solely on dietary intake (O'Donovan et al., 2017). Highly relevant to the current review is the work by Nielsen et al (Nielsen & El-Sohemy, 2012, 2014) who compared the effects of providing genotype-based dietary advice with general recommendations on behavioral outcomes. Participants in the intervention group were e-mailed a personalized dietary report providing recommendations for daily intakes of caffeine, vitamin C, sugar, and sodium based on genotypes for *CYP1A2, GSTM1* and *GSTT1, TAS1R2*, and *ACE*, respectively. Compared to the control group, participants in the intervention group more likely agreed that they understood the dietary advice they were given and the dietary recommendations they received would be useful when considering their diet. However, the intervention resulted in greater changes in only sodium intake compared to general population-based dietary advice.

Overall, the current evidence does not appear to provide strong support for genotype-based PN with respect to motivating behavior change. Moreover, there is some evidence to suggest that personal genetic knowledge might demotivate or increase anxiety (Hollands et al., 2016; Marteau et al., 2010; O'Donovan et al., 2017). Because DTC genotyping services to prescribe PN are already available, more research in this area is warranted. Study design, SNP selection, control group for comparison, outcome measures and clinical relevance need all be considered in research going forward(O'Donovan et al., 2017; Shyam & Smith). Fundamental to initiating this research is scientific evidence supporting genotype-based PN advice which is currently sparse(Guasch-Ferré et al., 2018).

5. CONCLUSIONS

Beverages are important sources of water, energy, vitamins and minerals and non-nutrients. With their widespread consumption, availability and contributions to diet and nutrition there is great interest in the role beverages play in health. Understanding factors contributing to drinking behaviors therefore has important public health and research implications. Genetics is amongst these factors and in the last decade progress has been made in this area. GWAS have confirmed known candidate loci but have also identified novel loci underlying alcoholic beverage and coffee drinking behavior. Many of these loci indirectly affect drinking behavior by modulating the physiological levels of bioactive constituents (i.e. acetaldehyde, caffeine). Several loci overlap with those associated with other metabolic traits such as obesity. Relatively less progress has been made in identifying loci underlying the habitual consumption of other beverages such as tea, juice, SSB and milk. Thus far, GWAS of beverage drinking behavior highlight an important behavior-reward component (as opposed to taste) to beverage choice and thus adds to understanding the link between genetics and beverage consumption and the potential barriers to dietary interventions. Loci identified via GWAS have been used in epidemiological research involving MR and G×D interaction analysis. An excerpt of findings were discussed in the current review and highlights the need for careful design and results interpretation and, importantly, replication. This research is necessary as it informs the clinical relevance of SNP-beverage associations and thus genotype-based PN. The latter has and will continue to attract much interest in the commercial and public health sectors.

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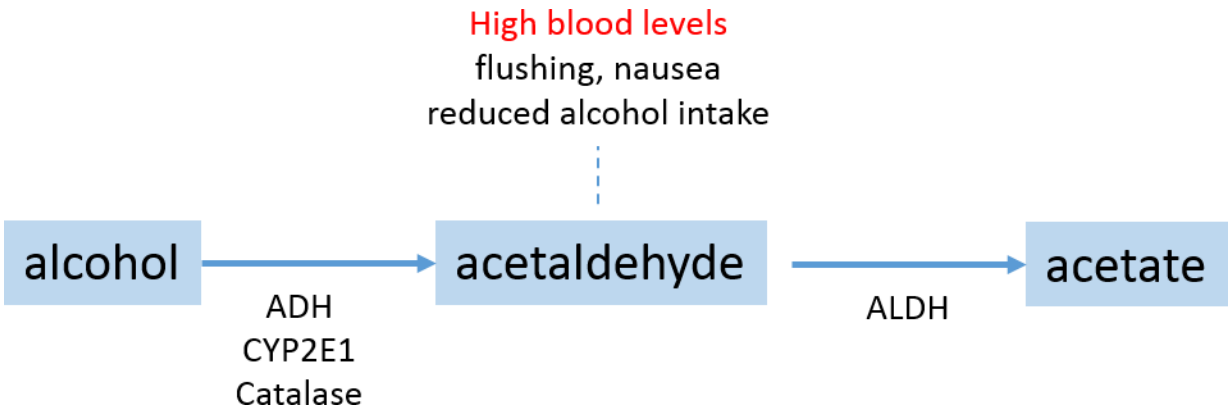

Figure 1.
Alcohol Metabolism

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Table 1.

Genome-wide association studies of beverage consumption reporting significant loci

Study Reference	Phenotype	Phenotype defined	Study design	N	Race
(Baik, I., Cho, Kim, Han, & Shin, 2011)	Alcohol drinking Alcohol Use Disorder (NULL)	Self-reported alcohol consumption among ever drinkers. Questionnaire, alcohol g/day in the past month, derived Alcohol Use Disorder Identification Test (AUDIT) score:, <8 or ≥8 score	Discovery Population-based males Replication Population-based males	1721 1113	Korean
(Takeuchi et al., 2011)	Alcohol drinking	Self-reported 'ever' vs 'non-drinkers' alcohol consumption Questionnaire, alcohol gou/wk also derived	Discovery Population-based Replication Health center-based	733 ca 729 co 2794 ca 1351 co	Japanese
(Schumann, G. et al., 2011)	Alcohol drinking	Self-reported alcohol consumption Self-reported alcohol consumption among ever drinkers (sex stratified) Questionnaire, alcohol g/day per kg (no detail)	Discovery 12 Population-based Replication 7 Population-based	26,316 21,185	EUR
(Yang, X. et al., 2013)	Alcohol drinking	Self-reported 'drinkers' (≥ 12 drinks in past year) vs 'non-drinkers' alcohol consumption In-person interviews. For drinkers, alcohol g/d also derived (NULL)	Discovery 1 population-based 1 community-based Replication 1 population-based	1420 ca 3590 co 4896 ca 13293 co	Chinese
(Kapoor, Manav et al., 2013)	Alcohol drinking	Maximum number of drinks consumed among drinkers In-person interview: "What is the largest number of drinks you have ever had in a 24-hour period"? (standard serving sizes per beverage).	Meta-analysis COGA: AD probands recruited through alcohol treatment programs; relatives of the probands and comparison families SAGE: non-overlapping COGA, Family Study of Cocaine Dependence (FSCD), and Collaborative Genetic Study of Nicotine Dependence (COGEND).	4915	EUR
(Quillen, E. E. et al., 2014)	Alcohol drinking	Maximum number of drinks consumed among drinkers in-person interview, AD: DSM-IV "What is the largest number of alcoholic drinks you have ever consumed in a day?" and "Does your face flush after drinking a little alcohol?"	One Sample Male AD probands and pedigrees from isolated region	272	Chinese
(Xu et al., 2015)	Alcohol drinking	maximum number of alcoholic beverages consumed in any lifetime 24-hour period ("MAXDRINKS") in-person interview	Discovery Yale-UPenn (recruited for studies of genetics of drug or AD, families and unrelated) Replication SAGE	2328 3215 2736 1276	EUR AFR EUR AFR
(Adkins et al., 2015)	Alcohol drinking	Mean alcohol intake over duration of follow-up (i.e. transition from adolescents to adulthood) trajectory estimate of alcohol consumption (drinks per week) across adolescence and early adulthood In-person interviews.	Meta-analysis Great Smoky Mountain Study (US, children) Christchurch Health and Development Study (CHDS): birth cohort children (New Zealand, 1977)	2126	EUR

Study Reference	Phenotype	Phenotype defined	Study design	N	Race
			Virginia Twin Study on Adolescent Behavioral Development: twin cohort US 1974–1983		
(Schumann, Gunter et al., 2016)	Alcohol drinking	Alcohol g/d among drinkers Heavy vs light/no drinking (NULL) Self-reported questionnaires/diaries In-person interviews	Discovery Meta-analysis Population-based Replication Meta-analysis Population-based	70,460 74,711 31,021 35,438	EUR
(Jorgenson et al., 2017)	Alcohol drinking	Individuals who reported drinking ≥1 day per week and ≥1 drink per day were defined as 'drinkers', whereas those who provided negative answers ('no days' and 'none') were considered as 'non-drinkers'. For alcohol drinkers, the regular quantity of alcohol drinks consumed per week was calculated by multiplying the two answers. Self-reported questionnaire	Meta-analysis Genetic Epidemiology Research in Adult Health and Aging (GERA) cohort : members of the Kaiser Permanente Medical Care Plan, Northern California Region (KPNC)	23,104 co 47,967 ca 2,673 co 4,374 ca 3,288 co 2,746 ca 1,165 co 1,310 ca	EUR Hisp/Latino East Asian AA
(Clarke et al., 2017)	Alcohol drinking	Alcohol units/week (excluded former drinkers) Sex-stratified GWAS Self-reported computer questionnaire	One-sample UK Biobank	112,117 (108,309 drinkers)	EUR
(Sanchez-Roige et al.)	AD	10-item AUDIT questionnaire (scores 0 to 40) Included only subjects who answered yes to the question 'Have you ever in your life used alcohol'.	One-sample 23andMe Direct to consumer genotyping service	20328 drinkers	EUR
(Gelernter, Joel et al., 2018)	Alcohol drinking	flushing, maximum number of alcoholic beverages consumed in any lifetime 24-hour period, and DSM-IV AD criterion count. Only alcohol-exposed subjects were included In-person interview	Meta-analysis Two samples of methamphetamine users, dependent subjects and exposed but not dependent	1045 drinkers	Thai
(Treutlein, J. et al., 2009)	AD	AD: based on DSM-IV criteria Interview	Discovery Male in-patients and population-based controls Replication Male in-patients and matched controls	476 ca 1358 co 1024 ca 996 co	EUR
(Kendler et al., 2011)	AD	abstainers excluded, alcohol factor scores among drinkers based on alcohol-related symptoms online questionnaire: Composite International Diagnostic Interview—Short Form, modified to screen for lifetime diagnoses	One sample, Race-strata survey-based recruitment	2,357 812	EUR AA
(Wang, K. S. et al., 2011)	AD	Discovery: DSM-IV diagnosis (interview) Replication: telephone diagnostic interview	Discovery Meta-analysis: COGA and SAGE Replication OZALC (family based)	1283 ca 1416 co 1650 ca 1684 co	EUR EUR
(Frank et al., 2012)	AD	DSM-IV criteria	Pooled sample analysis (males) extends Treutlien et al (2009) with more in-patients/ controls	1333 ca 2168 co	EUR

Study Reference	Phenotype	Phenotype defined	Study design	N	Race
(Zuo, L. et al., 2013)	AD	DSM-IV criteia for AD, controls: exposed to alchol but not addicted	Discovery: SAGE and COGA Replication OZ-ALC	1409 ca 1518 co 6438 European-Australian family subjects with 1645 probands	EUR
(Park et al., 2013)	AD	DSM-IV diagnosis interview Drinking habit questionnaire (controls)	Discovery cases: in-patients controls: non-alcoholics (hospital based) Replication cases: in-patients controls: “normal”	117 ca 279 co 504 ca 471 co	Korean
(Quillen, E. E. et al., 2014)	AD	DSM-IV diagnosis interview Other traits: Maximum number of drinks consumed among drinkers “What is the largest number of alcoholic drinks you have ever consumed in a day?” and “Does your face flush after drinking a little alcohol?”	One Sample Male AD probands and pedigrees from isolated region	102 ca 212 co	Chinese
(Gelernter, J. et al., 2013)	AD	Subjects were administered the semi-structured assessment for drug dependence and alcoholism (SSADDA) to derive DSM-IV diagnoses of lifetime AD	Discovery: 7 samples. Replication: 5 samples	2415 ca 1798 co 2669 ca 2002 co 324 ca 327 co 2269 ca 2975 co	AA AA EUR EUR AA AA EUR EUR
(Gelernter, J. et al., 2013)	AD score	AD symptom count (DSM-IV)	Discovery: 6 samples Replication: 5 samples	4629 5131 801 1746	AA EUR AA EUR
(Zuo, Lingjun et al., 2015)	AD	DSM-IV criteria Controls: exposed to alcohol but not addicted	Meta-analysis OZ-ALC SAGE + COGA SAGE + COGA Yale	1645 ca 3922 co 1409 ca 1518 co 681 ca 508 co 1429 ca 498 co	EUR EUR EUR EUR AFR AFR AFR AFR
(Chen, G. et al., 2017)	AD score	AD symptom count (DSM-IV)	One-sample SAGE	2605	EUR
(Treutlein, Jens et al., 2017)	AD	DSM-IV criteria Interview	One-sample Patients and community controls	1331 ca 1934 co	EUR
(Gelernter, Joel et al., 2018)	AD score	AD symptom count (DSM-IV) All alcohol-exposed subjects In-person interview	Meta-analysis	1045	Thai

Study Reference	Phenotype	Phenotype defined	Study design	N	Race
			Two samples of methamphetamine users, dependent subjects and exposed but not dependent		
(Cornelis, M. C. et al., 2011)	Caffeine	Total dietary caffeine, mg/d Self-reported, semi-quantitative FFQ.	Meta-analysis Five population-based studies in US	47,431	EUR
(Sulem et al., 2011)	Coffee	Cups/d among drinkers Self-reported, questionnaire or in-person interviews	Discovery 4 population-based, 1 genetic isolate Replication 2 population-based	6611 4,050	EUR EUR
(Amin et al., 2012)	Coffee	5 categories of intake Self-reported, semi-quantitative FFQ	Discovery 8 population-based Replication 1 population-based	18,176 7,929	EUR EUR
(Cornelis, M. C. et al., 2015)	Coffee	Cups/d among drinkers High vs low/non drinkers Self-reported, questionnaire or in-person interviews	Discovery 28 population-based Replication 13 population based 7 population based	91 462 30,062 7,964	EUR EUR AA
(Pirastu, Kooyman, Robino, et al., 2016)	Coffee	Cups/d Self-reported, questionnaire or in-person interviews	Discovery 2 genetic isolate populations Replication 1 genetic isolate	1213 1731	EUR EUR
(Nakagawa-Senda et al., 2018)	Coffee	Cups/d Self-reported, questionnaire	Discovery Replication Both samples drawn from the same multi-site population-based study	6312 4949	Japanese
(Pirastu, Kooyman, Traglia, et al., 2016)	Food/beverage liking	Liking/disliking scale (coffee, whole milk and beer amongst 20 items tested) Questionnaire administered by an operator	Discovery 3 genetic isolate populations Replication 1 genetic isolate 1 community sample	2240 1596	EUR EUR
(Pirastu et al., 2015)	Wine liking	Liking/disliking scale White and red wine tested Questionnaire administered by an operator	Discovery 3 genetic isolate populations Replication 1 genetic isolate 1 community sample	2240 1596	EUR EUR
(Zhong et al., 2018)	Total bitter beverages intake	Coffee (any type), tea (any type), grapefruit juice, beer/cider, red wine, spirit/liquor Servings/day, self-reported, questionnaire	Discovery UK Biobank Replication 3 US cohorts	85,852 39,924	EUR EUR
	Bitter alcoholic beverage intake	Beer/cider*, red wine, spirit/liquor Servings/day, self-reported, questionnaire	Discovery UK Biobank Replication 3 US cohorts	336,448 39,924	EUR EUR

Adv Food Nutr Res. Author manuscript; available in PMC 2020 February 28.

Study Reference	Phenotype	Phenotype defined	Study design	N	Race
	Bitter non-alcoholic beverage intake	Coffee (any type), tea (any type), grapefruit juice Servings/day, self-reported, questionnaire	Discovery UK Biobank Replication 3 US cohorts	85,852 39,924	EUR EUR
	Coffee intake	Any type (i.e., regular/decaf, instant/ground) Servings/day, self-reported, questionnaire	Discovery UK Biobank Replication 3 US cohorts	335,909 39,924	EUR EUR
	Tea intake	Any type (i.e., regular/decaf, herbal/non-herbal) Servings/day, self-reported, questionnaire	Discovery UK Biobank Replication 3 US cohorts	85,852 39,924	EUR EUR
	Grapefruit juice intake	Servings/day, self-reported, questionnaire	Discovery UK Biobank Replication 3 US cohorts	85,852 39,924	EUR EUR
(Zhong et al., 2018)	Total sweet beverage intake	Sugary carbonated beverages, flavoured juice beverages with sugar, any low-calorie or diet non-alcoholic beverages, pure fruit juice (excluding grapefruit juice), flavored milk, hot chocolate Servings/day, self-reported, questionnaire	Discovery UK Biobank Replication 3 US cohorts	85,852 39,924	EUR EUR
	Sugar sweetened beverages (SSBs)	Sugary carbonated beverages, flavoured juice beverages with sugar Servings/day, self-reported, questionnaire	Discovery UK Biobank Replication 3 US cohorts	85,852 39,924	EUR EUR
	Artificially sweetened beverages (ASBs)	Any low-calorie or diet non-alcoholic beverages Servings/day, self-reported, questionnaire	Discovery UK Biobank Replication 3 US cohorts	85,852 39,924	EUR EUR
	Pure non-grapefruit juices	Excluding grapefruit juice Servings/day, self-reported, questionnaire	Discovery UK Biobank Replication 3 US cohorts	85,852 39,924	EUR EUR

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Table 2.

Genome-wide significant loci for beverage consumption behavior

Locus	Closest gene(s)	SNP, EA	EAF				Race Origin	Trait	Effect	Reference	Assoc. with other traits
			AFR	AMR	ASN	EU					
1p35.2	*SERINC2*	rs4478858,G intronic	0.55	0.5	0.79	0.45	EU	AD	+	(Zuo, Lingjun et al., 2015; Zuo, L. et al., 2013)	
1q21.3	*ANXA9*	rs12405726, A intronic	0.09	0.5	0.43	0.36	EU	bitter non-alcoholic beverage intake	+	(Zhong et al., 2018)	serum urate
1q25.1	*KIAA0040, TNN*	rs6701037, C intergenic	0.33	0.32	0.09	0.46	EU	AD	+	(Wang, K. S. et al., 2011)	
1q25.1	*SERPINC1*	rs1799876, G intronic	0.86	0.35	0.6	0.33	EU	alcohol intake	−	(Xu et al., 2015)	
1q25.2	*SEC16B*	rs574367, T intergenic	0.09	0.15	0.19	0.21	EU	coffee intake	+	(Zhong et al., 2018)	BMI, obesity, menarche
2p25.3	*TMEM18*	rs10865548, G intergenic	0.93	0.85	0.9	0.83	EU	coffee intake	+	(Zhong et al., 2018)	BMI, obesity, weight, menarche
2p23.3	*GCKR*	rs1260326, T missense	0.12	0.41	0.56	0.41	EU/AFR	coffee intake	−	(Cornelis, M. C. et al., 2015; Zhong et al., 2018)	waist circumference, lipid traits, serum glucose, chronic kidney disease, C-reactive protein, gamma-glutamyl transferase, serum albumin, serum urate, leptin
							EU/AFR/ ASN/HL	alcohol intake, bitter alcoholic beverage intake	−	(Clarke et al., 2017; Jorgenson et al., 2017; Zhong et al., 2018) borderline (Schumann, G. et al., 2011)	
							EU	total bitter beverage intake	−	(Zhong et al., 2018)	
2p16.1	*MTIF2 - CCDC88A*	rs1437396,T intergenic	0.11	0.17	0.5	0.2	EU/AFR	AD		(Gelernter, J. et al., 2013)	
2p12	*CTNNA2*	rs140089781,A intronic	0.0	0.0	0.02	<0.01	EU	alcohol intake (men)	−	(Clarke et al., 2017)	
2q35	*PECR*	rs7590720,G intronic	0.25	0.26	0.31	0.29	EU	AD	+	(Treutlein, J. et al., 2009)	
3p12.1	*CADM2*	rs13078384,A intronic	0.02	0.20	0.02	0.33	EU	alcohol intake	+	(Clarke et al., 2017)	
4p14	*KLB,U6*	rs7686419,A intergenic	0.45	0.38	0.46	0.47	EU/AFR/ ASN/HL	alcohol intake	-	(Jorgenson et al., 2017)	
4p14	*KLB*	rs11940694,A intronic	0.38	0.61	0.57	0.40	EU	alcohol intake, bitter alcoholic beverage intake	−	(Clarke et al., 2017; Schumann, Gunter et al., 2016; Zhong et al., 2018)	

Locus	Closest gene(s)	SNP, EA	EAF				Race Origin	Trait	Effect	Reference	Assoc. with other traits
			AFR	AMR	ASN	EU					
4q22.1	*ABCG2*	rs1481012, A intronic	0.98	0.85	0.71	0.89	EU (AA)	coffee intake	+	(Cornelis, M. C. et al., 2015)	LDL, response to statin, serum urate, gout
								total bitter beverage intake	+	(Zhong et al., 2018)	
4q23	*ADH4-ADH7, ADH1A-C*	rs1229984,T missense	0.0	0.08	0.73	<0.01	EU/AFR/ ASN/HL	AD, AD symptoms, alcohol intake, bitter alcoholic beverage intake	−	(Clarke et al., 2017; Frank et al., 2012; Gelernter, J. et al., 2013; Jorgenson et al., 2017; Kapoor, Manav et al., 2013; Park et al., 2013; Treutlein, Jens et al., 2017; Xu et al., 2015)	esophageal cancer, upper aerodigestive tract cancers, oral cavity cancer, oropharynx cancer, pulse pressure
5q35.2	*CTB-33O18.3*	rs1363605,G intergenic	0.6	0.73	0.43	0.81	EU/AA	AD symptom count	+	(Chen, G. et al., 2017)	
6p21.33	*NRM*	rs2269705,A intronic	0.71	0.88	0.95	0.94	EU/AA	AD symptom count	−	(Chen, G. et al., 2017)	
6p21.32	*HLA-DOA*	rs9276975,T 3’ UTR	0.06	0.15	0.17	0.15	EU	white wine liking	+	(Pirastu et al., 2015)	
6q21	*PDSS2*	rs2216084,T intronic	0.96	0.64	0.99	0.67	EU	coffee intake	+	(Pirastu, Kooyman, Robino, et al., 2016)	
7p21.1	*AHR*	rs4410790,T intergenic	0.53	0.58	0.63	0.38	EU/AA	coffee intake	−	(Cornelis, M. C. et al., 2015; Sulem et al., 2011; Zhong et al., 2018) borderline (Nakagawa-Senda et al., 2018)	albuminuria
							EU	caffeine intake		(Cornelis, M. C. et al., 2011)	
							EU	bitter non-alcoholic beverage intake	−	(Zhong et al., 2018)	
							EU	total bitter beverage intake	−	(Zhong et al., 2018)	
7q11.22	*AUTS2*	rs6943555,A intronic	0.59	0.28	0.33	0.22	EU	alcohol intake	+	(Schumann, G. et al., 2011)	
7q11.23	*MLXIPL*	rs7800944,T intronic	0.61	0.82	0.89	0.72	EU	coffee intake	−	(Cornelis, M. C. et al., 2015; Zhong et al., 2018)	lipid traits
								bitter non-alcoholic beverage intake	−	(Zhong et al., 2018)	
7q11.23	*POR*	rs17685, A 3’UTR	0.13	0.22	0.35	0.30	EU/AA	coffee intake	+	(Cornelis, M. C. et al., 2015; Zhong et al., 2018)	
							EU	bitter non-alcoholic beverage intake	+	(Zhong et al., 2018)	

Locus	Closest gene(s)	SNP, EA	EAF				Race Origin	Trait	Effect	Reference	Assoc. with other traits
			AFR	AMR	ASN	EU					
							EU	total bitter beverage intake	+	(Zhong et al., 2018)	
7q31.1	*NRCAM*	rs382140, A intergenic	0.45	0.21	0.19	0.18	EU	coffee intake	+	(Amin et al., 2012)	
7q32.3	*PODXL*	rs2909678, C Intergenic	0.48	0.74	0.41	0.86	EU/AA	AD symptom count	−	(Chen, G. et al., 2017)	
11p14.2	*FIBIN*	rs145671205,C intergenic	0.04	0.07	0.06	0.07	EU	coffee liking	−	(Pirastu, Kooyman, Traglia, et al., 2016)	
11p11.2	*AGBL2*	rs7935528, A	0.14	0.34	0.35	0.42	EU	bitter alcoholic beverage intake	+	(Zhong et al., 2018)	
11q12.1	*OR8U8*	rs597045, A intergenic	0.97	0.82	0.86	0.69	EU	coffee intake	+	(Zhong et al., 2018)	
12q24.11-13	*ALDH2*	rs671, G missense	1	1	0.88	1	ASN	AD, AD symptoms, alcohol intake, flushing response	+	(Baik, I. et al., 2011; Frank et al., 2012; Gelernter, Joel et al., 2018; Jorgenson et al., 2017; Quillen, E. E. et al., 2014; Takeuchi et al., 2011)	lipid traits,, gamma-glutamyl transferase, serum urate, serum alpha-1-antitrypsin, esophageal cancer, hemoglobin, CHD, brain aneurysm, metabolic syndrome, BMI
							ASN	coffee intake	−	(Nakagawa-Senda et al., 2018)	
14q12	*AKAP6*	rs1956218, G intronic	0.68	0.66	0.44	0.53	EU	coffee intake	+	(Zhong et al., 2018)	
14q23.1	*ARID4A*	rs8012947, A intronic	0.27	0.3	0.62	0.28	EU	alcohol intake	+	(Clarke et al., 2017)	
15q24.1	*CYP1A1-CYP1A2*	rs2472297, T intergenic	0.02	0.09	0.0	0.24	EU/AA	coffee intake	+	(Amin et al., 2012; Cornelis, M. C. et al., 2015; Sulem et al., 2011; Zhong et al., 2018)	albuminuria, urine albumin,
								caffeine intake	+	(Cornelis, M. C. et al., 2011)	
								bitter non-alcoholic beverage intake	+	(Zhong et al., 2018)	
								total bitter beverage intake	+	(Zhong et al., 2018)	
16q12.2	*FTO*	rs55872725, c intronic	0.95	0.74	0.84	0.59	EU	SSB	+	(Zhong et al., 2018)	waist circumference, obesity, BMI, menarche, type 2 diabetes, adiposity, leptin

Locus	Closest gene(s)	SNP, EA	EAF				Race Origin	Trait	Effect	Reference	Assoc. with other traits
			AFR	AMR	ASN	EU					
17q11.2	*EFCAB5, NSRP1, SLC6A4*	rs9902453, A intronic	0.92	0.48	0.29	0.55	EU/AA	coffee intake	−	(Cornelis, M. C. et al., 2015)	
18q21.32	*MC4R*	rs66723169, A intergenic	0.11	0.13	0.2	0.23	EU	coffee intake	+	(Zhong et al., 2018)	BMI, obesity, height,
22q11.23	*SPECC1L-ADORA2A*	rs2330783, G intronic	0.92	0.98	0	0.99	EU	coffee intake	+	(Zhong et al., 2018)	
22q13.2	*CSDC2*	rs9607819, G intronic	0.74	0.52	0.91	0.81	EU	bitter non-alcoholic beverage intake	+	(Zhong et al., 2018)	

†GWAS catalogue traits unrelated to traits listed in column “Trait”