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NUTRITION

JUNE 2022

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Dashti HS, Chen A, Daghlas I, Saxena R. Morning diurnal preference and food intake: a Mendelian randomization study. *American Journal of Clinical Nutrition*. 2020;112(5):1348-1357.

What We Know, Think We Know, or Are Starting to Know

Our current scientific understanding shows a strong genetic influence on our time-of-day preferences, also known as our "chronotype" [1]. This genetic foundation interacts with our modern environment – artificial light, work schedules, trans-meridian air travel, social life timing – to influence our behavioural preferences for morning or evening.

Although we tend to think of chronotype and time-of-day preferences as the same, conceptually they are different. Chronotype is calculated using the midpoint of sleep as a marker for internal circadian timing, and therefore chronotype is considered a *biological* construct, rather than a *psychological* construct or personality *trait* [2]. However, diurnal preference [diurnal meaning 'of the day'] is conceptualised as a *behavioural trait*, and is usually distinguished as a preference for 'morningness' or 'eveningness' [3,4].

As such, diurnal preference between 'morningness' and 'eveningness' has been suggested to better account for variation in behaviours corresponding to time of day, like preferred time of activities or for performance [3]. Recent genetic database research has suggested a shared genetic basis for both diurnal preferences and personality traits [5].

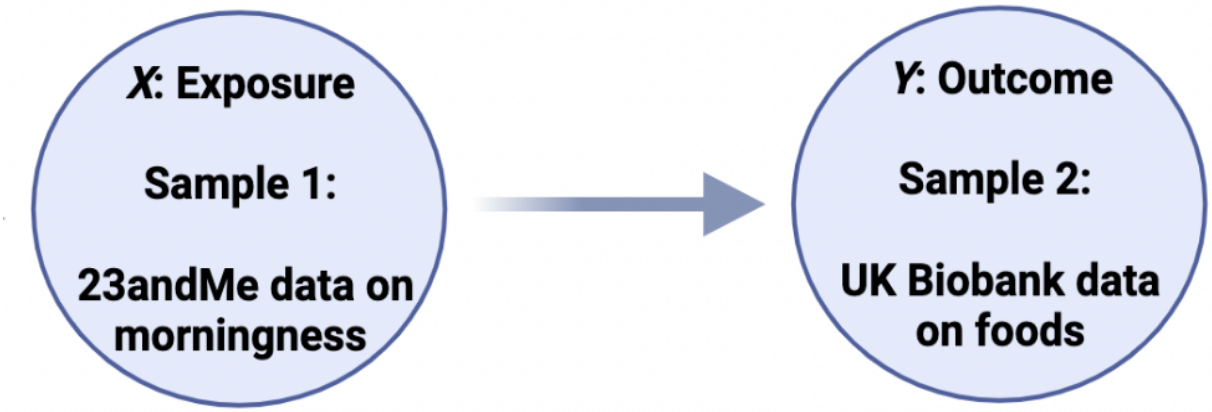
For example, people with a preference for 'morningness' exhibit higher levels of the trait conscientiousness and agreeableness, but lower levels of extraversion [6]. This, of course, makes it all a bit of a tangled web to determine what is influencing what when it comes to diet; is it behaviour traits, genetics, both?

The Study

The investigators conducted a two-sample Mendelian Randomisation* [MR; *see Geek Box, below] investigating the associations between genetic predisposition to a morning preference and intakes of specific foods. A "two-sample MR" is a type of MR where the exposure is measured in one genetic sample and the outcome is measured from another genetic sample. Thus, the present two-sample set up in this study was:

- Exposure: 23andMe data on 'morningness'
- Outcome: UK Biobank data on 61 food variables

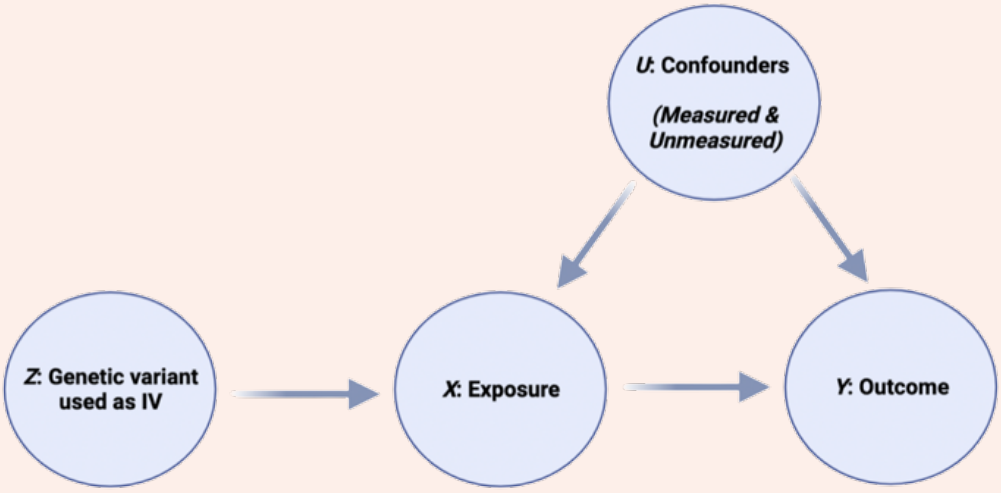
The following figure further illustrates the concept of a two-sample MR:



Thus, the analysis was investigating the association between the genetic variants related to morning diurnal preference [from 23andMe data] and the intakes of 61 food variables [from Biobank data].

*Geek Box: Assumptions of Mendelian Randomisation

All MR studies start with a genetic variant, which for an MR is known as an "instrumental variable", or IV. The best way to illustrate these concepts is with the use of 'directed acyclic graphs', or DAG. DAG are graphs which illustrate the direction of relationships and are useful to illustrate causal concepts. Here is a DAG for MR:



*In this illustration, **Z** is the IV, a genetic variant associated with **X**, where **X** is the risk factor or "exposure". For example, **Z** could be a genetic variant which results in more LDL-receptors, which means that **X** would be low blood LDL-C levels. **Y** is the outcome, in this example, CVD. Thus, this graph is depicting the causal effect of **X** [low LDL-C] on **Y** [CVD]. Finally, **U** is any unmeasured confounder, i.e., "residual confounding". So, an MR study uses an IV [**Z**] to act as a proxy for an intervention of X on outcome **Y**.*

*For an IV [**Z** in our graph above] to be valid, it must meet three assumptions:*

1. ***Relevance:** The genetic variant, **Z**, is robustly associated with the risk factor, **X***
2. ***Exchangeability:** The genetic variant is independent of confounders, **U***
3. ***Exclusion-restriction:** The genetic variant has no effect on the outcome, **Y**, i.e., **Z** only influences **Y** through the exposure, **X**.*

An IV is only valid where the 3 assumptions above hold. This is crucial, because it means that claims of "causality" can only be made where these assumptions are met. However, in practice there is no easy way of testing that all assumptions hold, unlike in other statistical methods where the assumptions can be tested [e.g., the assumption that data follows a normal distributed can be tested with both statistical tests and by visual inspecting normality graphs].

*In reality, the assumptions are addressed by considering different factors, e.g., the biological plausibility of the IV [i.e., is it biologically plausible that a gene that effects the LDL-receptor would lower LDL-C levels], by examining whether the estimates of the effect of the risk factor **X** on the outcome **Y** are similar across different analyses [i.e., does low LDL-C from different LDL-receptor variants have similar effects on CVD], and by considering whether the effects are not modified by other factors.*

Results: In total, the genetic variants from 23andMe were derived from a sample of 240,098 participants and 361,194 from the UK Biobank cohort.

- ***Food Intake:*** A morning diurnal preference was associated with increased intakes of alcohol with meals, bran cereal, cereals, dried fruit, fresh fruit, and water) [all square points to the right-side of the 0 line in the **figure**, below].

Specifically, a 1 h earlier midpoint of sleep was associated with 0.49 pieces of fruit more per day, and 0.58 bowls more per week cereal.

Morning diurnal preference was also associated with lower weekly beer/cider intakes, full cream milk, processed meat, other cereals [e.g., Crunchy Nut Cornflakes, Coco Pops, etc.], and lower variation in diet [all square points to the left-side of the 0 line in the **figure**, below].

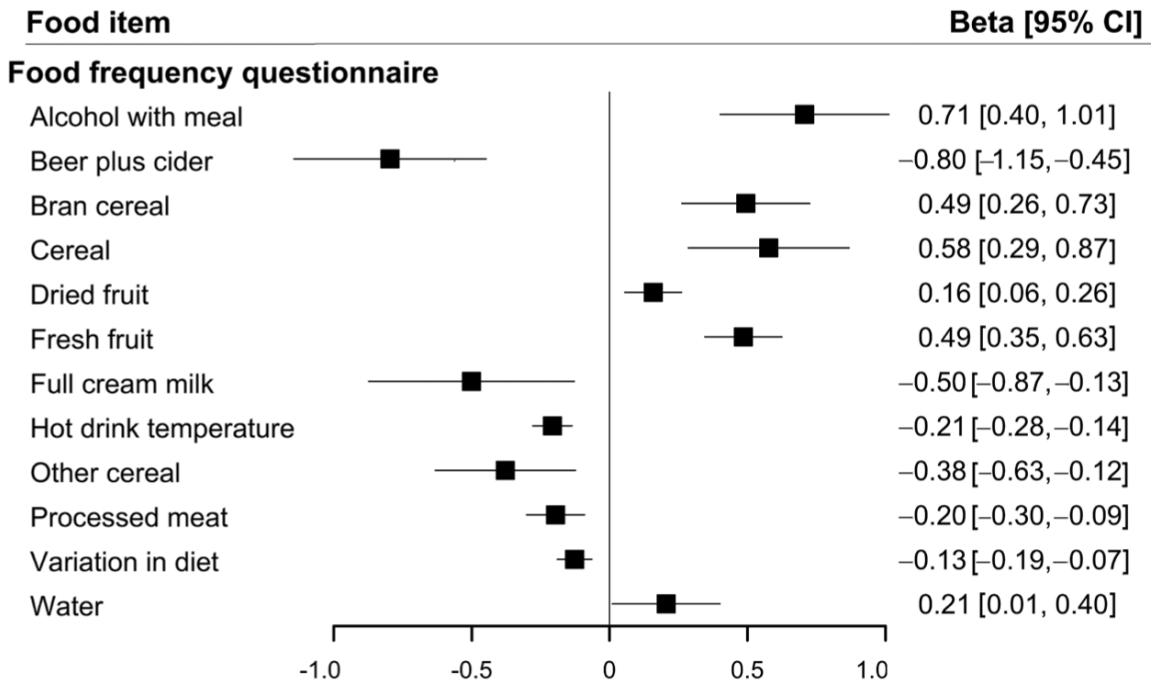


Figure *from the paper illustrating the significant genetic associations for dietary variables in the present study. In this analysis, a morning diurnal preference was represented as a 1 h earlier midpoint of sleep. The Beta and 95% CI represent differences in portions or odds [which is slightly confusing, because they are communicating different information]. For example, if you look at 'cereal', this was expressed in bowls per week; thus the finding indicates that each 1 h earlier midpoint of sleep was associated with 0.58 [and a 95% CI of 0.29 to 0.87] more bowls of cereal per week.*

The Critical Breakdown

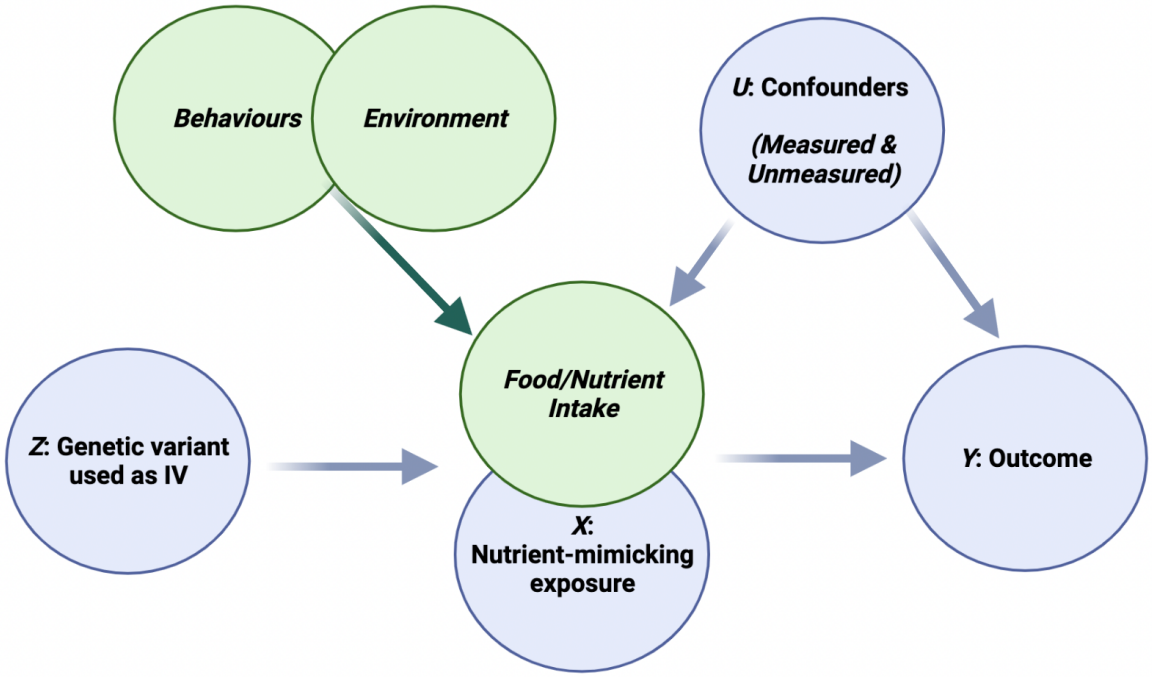
Pros: The study had a vast data set from two large, unrelated population samples; this is one of the main advantages of two-sample MR. Thus, the study was highly powered to detect associations between 'morningness' and the selected food variables. The genetic variants for a morning diurnal preference are robust, derived from genome-wide association studies [GWAS]. The food variables were derived from UK Biobank food-frequency questionnaire, but a further 24 h recall was also collected in a subset of 211,036 Biobank participants. This allowed both a comparison between the genetic variants and food items from both FFQ and 24HR to be investigated, and for the analysis to investigate whether there were any differences in the associations between workdays and weekends. A sensitivity analysis also excluded participants who reported working some nightshifts.

Cons: The two samples were confined to participants of European ancestry, and in the case of the UK Biobank, White British ancestry, and the findings should not be generalised beyond these groups as ethnic differences in diurnal preferences have been demonstrated [(7)]. The analysis itself was limited to 61 food variables, from which 11 reached a statistically significant association, i.e., reflecting the fact that dietary choices are not merely a genetic output. The analysis also used the midpoint of sleep as the marker of diurnal morning preferences, and this may be overlapping two constructs [more under Relevance, below]. Ultimately, although highly statistically significant, the outcomes are also relatively paltry: a strong genetic predisposition in the morning might mean you eat half a banana more.

Key Characteristic

The most challenging assumption to meet for a valid causal conclusion from MR is assumption no.3 – "exclusion-restriction" – that the genetic variant only influences the outcome through the exposure of interest. Put another way, this assumption is violated when the genetic variants [in this case for morning diurnal preference] also affects other genetic traits that influence the outcome independent of the exposure [morning diurnal preference].

To highlight this by way of an example from the present study, we would say that the selected genes only influence fruit intake in the morning through having a morning diurnal preference. Can you see how this starts to get difficult for dietary exposures? The "exclusion-restriction" assumption relates to the potential relationships *between genetic traits*. But we know that food intake is only weakly influenced by genetic factors, and more strongly influenced by situational factors: behaviours and the environment [8,9]. Take a look at this **figure** below to illustrate this concept:



And this is *really* important to think about "causal" claims from MR, because if there is a separate behaviour that could directly influence the outcome, the assumptions of MR are violated [8]. Put it this way, could you think of any other behavioural reason why someone would eat fruit in the morning, whether they had a morning diurnal preference or not? Of course you can. So, once again this is your friendly reminder that when it comes to this emerging area of genetic analysis and diet, beware the *"perils of hasty causal expectations"* [9].

Interesting Finding

As stated above, if there are separate behaviours that influence an outcome, the key assumptions of MR do not hold. The challenge here is that diurnal preferences are correlated with several behavioural traits. The 'Big Five Factor Inventory' personality dimensions include Extraversion [talkative, assertive, energetic], Agreeableness [good-natured, cooperative, trustful], Conscientiousness [orderly, responsible, dependable], Emotional Stability [versus neuroticism, i.e., calm, not easily upset, not neurotic], and Openness [intellectual, independent-minded] [10].

Of these, a morning diurnal preference is most consistently associated with higher levels of Conscientiousness and Agreeableness, and lower levels of Openness [6]. Could these personality traits perhaps influence dietary habits? Conscientiousness has been associated with breakfast consumption, and chronotype [i.e., earlier chronotype] was shown to mediate the relationship between positive attitudes toward breakfast consumption and personality traits [11]. Indeed, Conscientiousness correlates with fruit and vegetable consumption in adults and adolescents [8,12].

This is an example of how the assumptions of MR may not hold. This is not a fatal blow to the study, however; it means that where these assumptions do not hold the findings should be interpreted as genetic associations, not cause-effect relationships.

Relevance

It is important to stress that there may be a shared genetic basis for diurnal preferences and related personality traits [5]. Recall that chronotype itself is conceptualised as a state [i.e., reflecting interactions between an individual attribute and the environment], rather than a trait [i.e., an attribute of an individual independent of situational effects] [2].

Thus, while morning diurnal preference may strongly be influenced by genetic predisposition, there are other behavioural/personality traits that also correlate strongly with diurnal preference [3]. It is therefore not possible to say that the findings of the present study represent a cause-effect relationship between a morning diurnal preference and intake of specific foods.

To be fair to the authors, they use cautious language in describing their findings as *"potential causal links"*, which is refreshing to see and probably reflects the fact that this paper was published in *AJCN* rather than *Nutrients*.

Ultimately, there are three conceptually distinct but highly correlated concepts at play here: chronotype, diurnal preference, and personality traits. The present study investigated genetic diurnal preference for morning, with morning preference associated with small changes in intakes of specific foods. However, while diurnal preference and personality traits associated with diurnal preference may have a similar genetic basis, personality traits are not exclusively derived from diurnal preference and influence dietary intake *per se* [although potentially mediated by chronotype] [8,11,12].

In sum, the present study leaves us with *genetic associations* between a morning diurnal preference and certain health-promoting dietary characteristics, in particular higher fruit, cereal grain and bran intakes, and lower full cream milk and processed meats.

Application to Practice

To put this back in context, let us bear in mind that behaviours and the environment have a stronger influence on dietary intake than genes [8,9]. This is important when we think about the actual magnitude of effect found in the present study, which was relatively miniscule. For example, a genetic predisposition to a morning diurnal preference may lead to you eating an extra half-apple a day and two-thirds a bowl of cereal a week.

Even if we assumed for present purposes that this was a causal relationship, for people without a morning diurnal preference it is hardly such a deficit that could not be overcome through behavioural changes. Not having a genetic morning preference is hardly going to prevent someone eating half a piece of fruit.

Genetics is sexy right now. "Personalised nutrition" is the hot ticket. And yet with all of that, and without any of it, the lowest hanging fruit – pun intended – has not even been picked when it comes to helping people at the population level, or individual level, improve diet for health-gain. Genetics may be the reason you like to wake earlier in the morning, but they are not the reason you can or cannot eat fruit.

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