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

Back in November, we covered a concept known as [‘social jetlag’ in a Deepdive]. In today’s Deepdive, we’re going to delve back into this world of circadian-related environmental exposures to look at the associations between ‘chronotype’, meal timing, and risk for obesity. Why might this be an important exposure to consider? Because we are *all* ‘exposed’, so to speak, by virtue of being a mammal on a planet with a 24 h rotation on its axis, meaning a daily cycle of light and darkness*.

So, what is your ‘chronotype’? Literally translated as ‘time type’, this is an individual’s behavioural expression of preferences for sleep-wake timing, often colloquially referred to as ‘morning larks’ or ‘night owls’ [(1)]. This behavioural expression reflects an individuals’ *internal biological timing* [(1)]. This is an important part of the concept: chronotype is a *biological construct*, rather than a psychological construct or personality trait [(2)].

As such, chronotype is strongly influenced by genetics [(3)]. However, there are two other factors which interact with genetic predisposition to influence someone’s chronotype: a) the strength of “time-cues”, i.e., environmental signals, like light, which provide an indicator to the circadian system to synchronise to the time of day, and; b) age [(2)].

For example, the strength of exposure to light influences an individuals’ internal biological clock; weak light strength [e.g., urban environments, indoor lighting, lack of daily natural light exposure] results in the phase of the internal clock *delays*, in a chronotype-dependent manner [remember, genetics!] [(4)]. Conversely, when the environment emits strong time-cues [e.g., natural light conditions] the internal clock *advances*, again in a chronotype-dependent manner, by an average of 30min per 1 h of outdoor daytime light exposure [(1,2,4)].

What of age? Adults aged 21–30yrs of age exhibit the latest midpoint of sleep during work days, adults >31yrs and adolescents <21yrs having an earlier midpoint of sleep [(1)]. On free days, however, there is substantial differences between age groups, with adolescents delaying sleep by 3 h, adults 21–30yrs by ~2 h, and adults >31yrs by ~1 h [(1)].

Chronotype is measured as the midpoint of sleep, using calculations that correct for sleep debt that may accumulate during the working week, when people tend to have enforced wake times [(1)]. It is this midpoint of sleep which is used to distinguish chronotypes. Thus, early [morning] chronotypes exhibit an earlier sleep phase, preference for waking earlier in the morning, and feel most alert and active during the early part of the day, while late [evening] chronotypes display a delayed sleep phase, preference for later rising, and feel most alert and active in the evening or night [(1,2,4)].

Observational associations of between evening energy intake and adverse metabolic health outcomes [5–7] have not been supported by interventions testing the initial hypothesis: that lower morning energy intake or breakfast skipping led to compensatory calorie intake later in the day [8,9]. This has led to interest in the role of factors like chronotype, as discordance between internal biological rhythms in metabolism and the timing of food intake may combine to increase metabolic risk [10]. The present study investigated the associations between morning and evening energy intake and risk for obesity, and whether any such effect was mediated by chronotype.

*Geek Box: Basis of Circadian Rhythms

So, how and why do we even have a chronotype in the first place? It's one of the cooler aspects of human biology, and indeed the biology of nearly all organisms on the planet. It is because of the planet we evolved on, and the fact that every day, this globe revolves around an axis with a period of 24 h. Within this 24 h rotation, there is a light phase – when we're facing the sun – and a dark phase – when we rotate away from the sun. The exact period of light depends on the season, which relates to the Earth's revolving around the sun, and the latitude of the specific place you are on the planet. Virtually all organisms on the planet have evolved internal, biological rhythms to synchronise the timing of different physiological processes and related behaviours to the Earth's daily rotation. If we were to take you and put in a blacked-out bunker or cave, with no light or other time-cues, your circadian rhythms would still run with the same pattern, however, they would not be exactly 24 h in length [with interindividual and ethnic differences, the range of the free-running period may be between 23.7 h – 25.0 h]. To synchronise these rhythms to the exact 24 h period of the Earth's rotation, organisms like ourselves rely on signals from the environment, of which light is the most potent. Specialised cells in your eyes have evolved with exquisite sensitivities to different intensities and spectral compositions of light, and there is a dedicated pathway going from the retina to a densely concentrated connection of neurons in the hypothalamus, known as the suprachiasmatic nucleus, or SCN for short. This is known as the 'central clock'. However, extending how fascinating the circadian system is, every single cell in your body has its own internal "clock". These circadian clocks in organs and tissues, like the digestive tract, liver, adipose tissue, skeletal muscle, etc., are known as the 'peripheral clocks'. We now know that these peripheral clocks can shift, independent of the central clock, in response to other time-cues, in particular meal timing. Humans are diurnal mammals, meaning that we are active during the day. Conversely, our mammalian cousins, rodents, are nocturnal, and their active phase is during our dark phase, i.e., night-time. The timing of food intake, when aligned to the daytime, waking and active period, serves to reinforce the synchrony of circadian rhythms with the appropriate time of day. However, characteristics of modern society brings into collision both disruption to the circadian system [e.g., artificial light exposure, 'social jetlag'] with traditional risk factors for cardio-metabolic disease [e.g., energy-dense food, ubiquitous food supply availability]. Consequently, the interaction between circadian rhythms and the modern environment may be important for metabolic health.

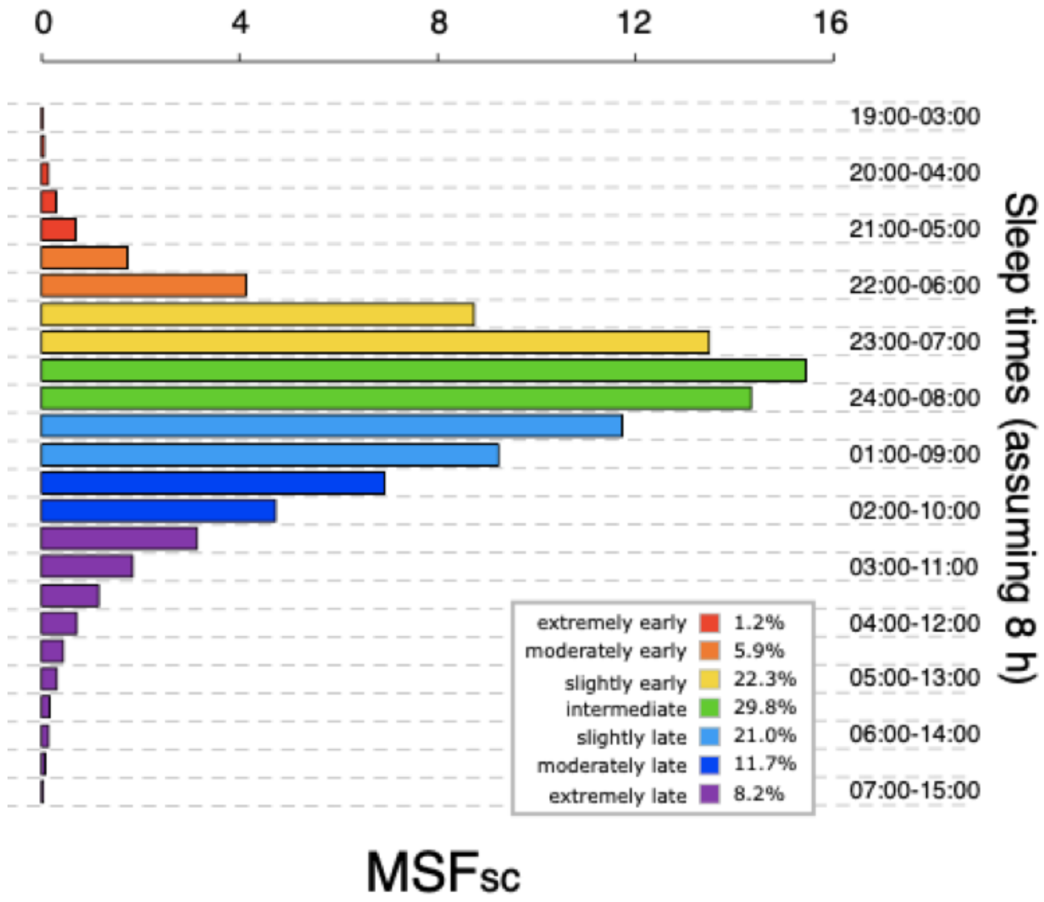

Figure *Roenneberg et al.*[(2)] *illustrating the distribution of chronotypes, measured as the midpoint of sleep corrected for sleep debt. The left Y-axis, with 8 h time slots, is* <u>*not*</u> *the midpoint of sleep, but indicates what the ideal 8 h sleep-wake cycle would be for the corresponding chronotype. For example, if your midpoint of sleep was 3am, you would be in the yellow bars above ("slightly early"), with around 22.3% of the general population. This would mean that your likely ideal sleep-wake cycle would be between 10 and 11pm to 6 or 7am.*

The Study

The study sample was recruited from the US AARP cohort, with residents in Pittsburgh, Pennsylvania. Participants were excluded if they were currently on a weight loss diet, had a BMI <18.5 or >40, or history of cardio-metabolic disease.

Participants completed an online 24 h dietary recall, once every two months across an entire year. The time of each eating episode was recorded during the dietary assessment. The "morning" eating window was defined as the first two hours after rising, and "night" eating window as the two hours prior to bedtime. The energy consumed in each time-bin was calculated as the percentage of total daily energy intake occurring in that eating window, and divided into quintiles [fifths]. The analysis then compared the highest to lowest energy intakes in those time-bins in the overall cohort, and then stratified according to chronotype.

Height and weight were measured at three in-person clinical visits in the 1st, 7th, and 12th month of the year of the study, from which BMI was calculated. Chronotype was calculated using the Munich Chronotype Questionnaire [MCTQ].

Results: 872 participants were included in the final analysis. 67% of participants had completed all six 24 h recalls, and 94% completed at a minimum of three. The recalls covered an average of 3.7 weekdays and 1.5 weekend days.

- ***Meal Timing and BMI*:** Examining all participants together, those with the highest proportion of daily energy consumed during the morning [i.e., within 2 h of waking] had 47% lower odds [OR 0.53, 95% CI 0.31 to 0.89] of overweight/obesity. Conversely, the highest proportion of energy during the night-time window [within 2 h of bed] was associated with 82% higher odds [OR 1.82, 95% CI 1.07 to 3.08] of overweight/obesity.

- ***Morning Energy Intake and Chronotype Interaction*:**
    - **Morning Energy Intake [within 2 h of waking]:** In *early chronotypes*, the highest morning energy intake was associated with 68% lower odds [OR 0.32, 95% CI 0.16 to 0.66] of overweight/obesity. However, with *late chronotypes*, there was no significant effect of high morning energy intake.

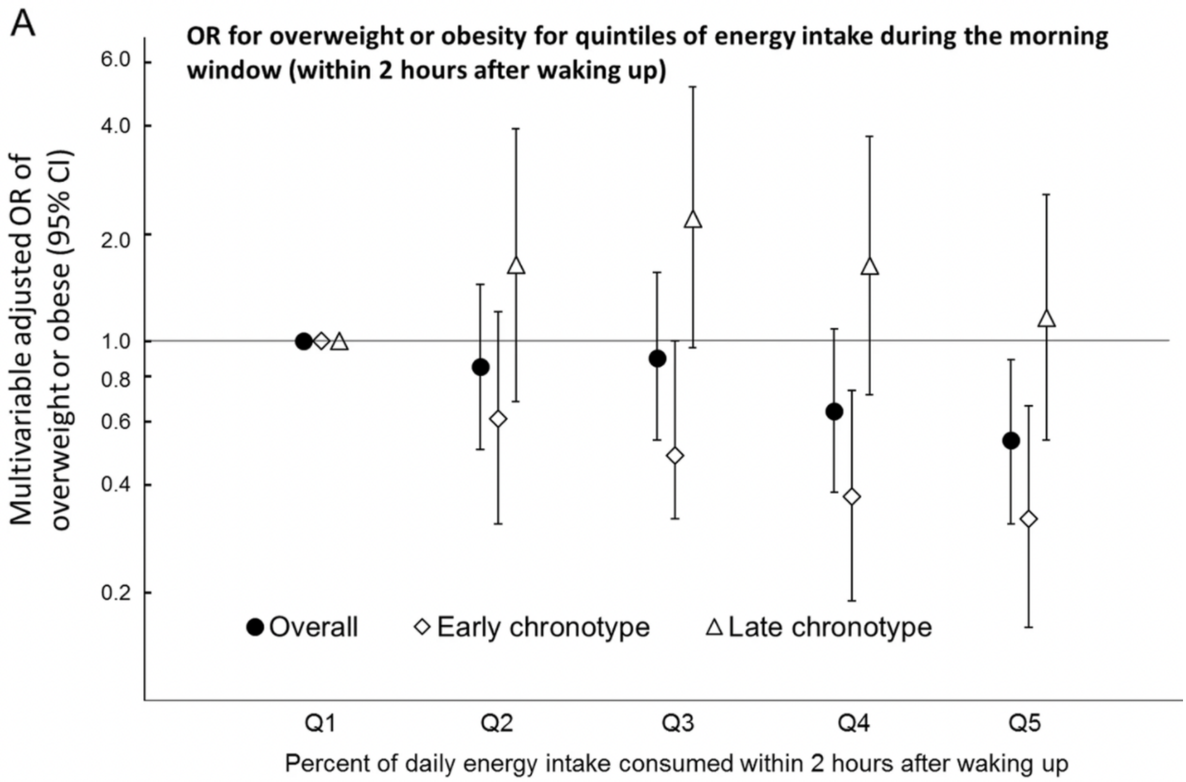

Figure the paper illustrating the odds for overweight/obesity according to different levels of energy intake in the morning [within 2 h of waking] and stratified by chronotype. The solid black circles represent the overall cohort; you can clearly see that with increasing percentage of daily energy consumed in this time window, the risk of higher BMI decreased. But now look at the difference according to chronotype; the open diamonds represent early chronotypes, and you can clearly see that the magnitude of the effect of high early morning energy intake is much greater, and more linear, in this group. Conversely, in the late chronotypes, shown as open triangles, the highest level of energy intake showed no significant protective effect. As you can see from the confidence interval arms for the Q5 in late chronotypes, they are fairly spread across the 1.0 line, i.e., not significant but also not really clear in direction of effect.

- **Night Energy Intake [within 2 h of bed]:** In *early chronotypes*, the highest level of energy intake was not significantly associated with higher BMI. However, in *late chronotypes*, the highest level of energy intake in this window was associated with a near 5-fold higher odds [OR 4.94, 95% CI 1.61 to 15.14] of overweight/obesity.

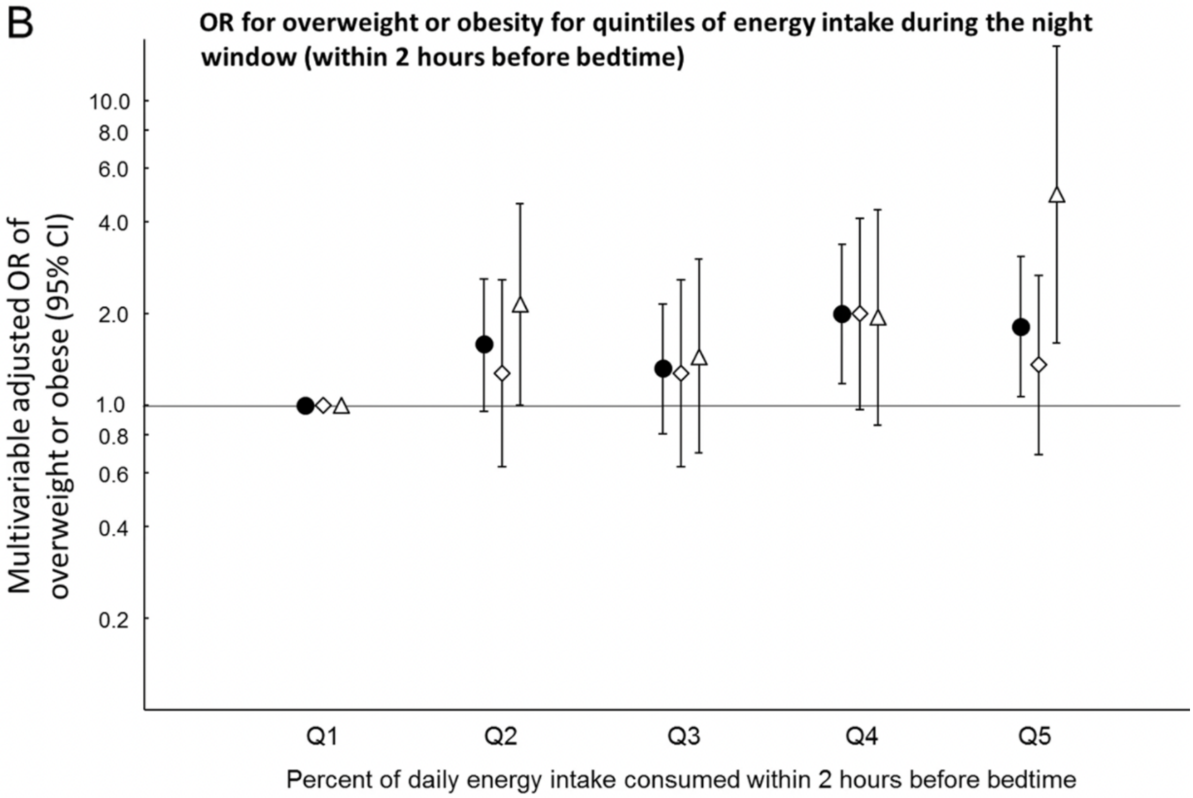

Figure from the paper illustrating the odds for overweight/obesity according to different levels of energy intake in the night [within 2 h of bed] and stratified by chronotype. The solid black circles represent the overall cohort; you can also clearly see that with higher percentages of daily energy consumed in this time window, particularly in Q4 and Q5, the risk of higher BMI increased. But again let's look at the difference according to chronotype; the open diamonds represent early chronotypes, and you can see that there appears to be a trend toward higher risk, but this is not significant. Conversely, in the late chronotypes, shown as open triangles, the highest level of energy intake was associated with a significant increase in risk.

- ***Macronutrient Intake and Chronotype Interaction*:** In *early chronotypes*, the highest level of protein and carbohydrate intake in the morning were associated, respectively, with a 61% [OR 0.39, 95% CI 0.19 to 0.81] and 80% [OR 0.20, 95% CI 0.10 to 0.42] odds for overweight/obesity. In *early chronotype*s, there was no associations between night-time macronutrients and risk. In *late chronotypes*, carbohydrate intake and sugar were associated with 4-fold and 3-fold higher odds for overweight/obesity, respectively.

The Critical Breakdown

Pros: Administering up to six 24 h recalls would be expected to substantially reduce the potential for within-person error and misclassification [11]. Further, differences in diet between workdays and free days could also introduce variation, both within-person and between-person variation, so having data for both weekdays and weekend days is a positive. The analysis used a robust assessment of circadian phase, i.e., the midpoint of sleep calculating using the MCTQ, which has been shown to correlate strongly with objective laboratory measures of melatonin [12]. The analysis was also based on individual sleep-wake timing, which would provide a more representative proxy for individual *biological timing*, rather than the clock time [more under ***Key Characteristic***, below]. The study cohort was balanced nearly 50:50 for men and women.

Cons: The adjustment model was fairly light as far as potential confounders which could influence the results, for example smoking, natural light exposure, and social jetlag. The stratification of time-bins, looking at the supplementary data, could mean that the associations with the 'night' time-bin [i.e., within 2 h of bed] could reflect some carryover effect from the previous time-bin [which was defined as the midpoint of the waking period up to 2 h before bed]. This was the peak of energy intake for all participants, with 45% and 47% of daily energy in this time-bin in early and late chronotypes, respectively. Although there were no significant associations with the outcomes in this time-bin in either chronotype, this does not mean food consumed in that period disappeared before bed. Bear in mind post-prandial metabolism, depending on the size of the meal, may extend to up to 6-10 h depending on the size of the meal [13]. If we assume that internal circadian phase may have a role to play [more under ***Key Characteristic***, below], then I' m not sure we can assume the association in the 'night' time bin is entirely independent of the previous energy intake.

Key Characteristic

Recall that the 'morning' time-bin was defined relative to an individual' s wake time, and the 'night' time-bin was defined relative to their bedtime. This would provide a more representative proxy for individual *biological timing*, rather than the 'clock time'. Why? Well, recall that chronotype is an individual' s behavioural expression of *sleep-wake timing* preferences. If my preference is 9pm-5am, and yours is 12am-8am, then my midpoint of sleep is ~1am and yours is ~4am. Big difference!

Yet *both* of our internal physiological processes would be synchronised to the same 24 h day. What would differ would be the *phase* of each our synchronising, i.e., my rhythms would run earlier and yours would run later. My melatonin could rise at 7pm and yours at 10pm. This would correspond to differences in our insulin sensitivity, glucose tolerance, energy expenditure, gastrointestinal motility, and lipid metabolism, at different times of day [14,15]. And these differences could be missed if we were to just look at 'clock time', i.e., "9am", because the *biological meaning* of that time, in terms of our underlying metabolism and physiology, would be different. For why this may be relevant for metabolic health, keep reading for more under ***Relevance***, below.

Interesting Finding

There is a lot of food for thought arising from the finding that in late chronotypes, higher morning energy intake appeared to confer no protective effect against higher adiposity. And this even though, on average both early and late chronotypes consumed roughly the same proportion of daily energy within 2 h of waking [13.7% and 15.0%, respectively]. Why could breakfast be protective in early chronotypes, but not late chronotypes?

There are several factors which could be at play. The first is genetics; In a recent study investigating the heritability of food timing among 56 pairs of twins, *Lopez-Minguez et al.* (16) showed there was a 56% heritability for breakfast timing and 38% heritability for lunch, but no such heritability for dinner timing. This suggests that, while earlier temporal energy intake may have a strong genetic component, evening energy intake may be influenced by behavioural factors and preferences (16).

The second is personality traits and related health behaviours. 'Big Five' factor personality traits such as conscientiousness have been associated with breakfast consumption, and chronotype has been shown to mediate the relationship between attitudes toward breakfast consumption and personality traits, i.e., people with a morning preference may exhibit more health-promoting behaviours related to personality traits like conscientiousness (17). Breakfast consumption also correlates strongly with wider health-promoting behaviours (18), and evening chronotype has been associated with several negative health related behaviours, including low diet quality, higher prevalence of smoking, and less physical activity (19,20).

In the present study, smoking was not adjusted for, there were no significant differences in diet, and while late chronotypes did exhibit lower physical activity levels, this was adjusted for. Nevertheless, there are a number of genetic, behavioural, and environmental factors which may conspire against late chronotypes, even when they diligently get their breakfast in.

Relevance

A point I will always hammer home in relation to this field is that it is *very early doors*. Most of the 'sexy' evidence is in rodents (21). Much of the human evidence is cross-sectional, and we still don't quite have a firm grasp on what exactly chronotype and social jetlag represent as exposures.

Yes, we know can define what chronotype and social jetlag *are*, and how to calculate them, but what does it mean as an environmental exposure? Do they represent more sleep disruption, and the adverse health effects of impaired sleep? Are the associations with diet more a reflection of the impact of sleep curtailment on diet? For example, a study that restricted sleep by just 90min per night over two weeks found that participants significantly increased energy intake from snacks and redistributed energy intake to the evening (22).

One fascinating element, for which we currently only have three cross-sectional studies to go off (23–25), is the relationship between energy intake and proximity to an individual's *internal biological night*. Recall the analogy under Key Characteristic, above: my sleep-wake preference is 9pm-5am, and yours is 12am-8am. This means the timing of our melatonin onset, which signals the beginning of the *biological night* [rather than just clock time], would differ, e.g., my 'biological night' could start at 8pm clock time while yours could start at 11pm clock time.

A couple of recent cross-sectional studies have shown that energy intake occurring in closer proximity to melatonin onset was associated with significantly higher body fat levels [23,24]. What is *really* interesting is that these associations were *not evident* when analysing energy intake only in relation to clock time. So, it could be that these associations have more to do with the biological, rather than social, clock.

Application to Practice

Is there hope for the poor late chronotypes? Yes, there is. One is the increasing prevalence of work-from-home since the pandemic started, with evidence showing that people increased sleep duration, slept more in line with personal preferences, and reduced social jetlag levels [26]. The second is that a recent, interesting intervention [which may find itself in a Deepdive] tested what they termed a 'chronotype-adjusted diet' [27]. They found that tailoring the distribution of energy according to chronotype resulted in equally effective weight loss in both early and late chronotypes. The message so far in this research is, wherever possible, try to align behaviours and the social clock as much with your internal preferences as much as possible. Living against the biological clock may carry risks.

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