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Brain structural covariance network differences in adults with alcohol dependence and heavy drinking adolescents

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Background and aims. Graph theoretic analysis of structural covariance networks (SCN) provides an assessment of brain organization that has not yet been applied to alcohol dependence (AD). We estimated whether SCN differences are present in adults with AD and heavy drinking adolescents at age 19 and age 14, prior to substantial exposure to alcohol. **Design.** Cross-sectional sample of adults and a cohort of adolescents. Correlation matrices for cortical thicknesses across 68 regions were summarized with graph theoretic metrics. **Setting and participants.** 745 adults with AD and 979 non-dependent controls from 24 sites curated by the ENIGMA-Addiction working group, and 297 hazardous drinking adolescents and 594 controls at age 14 and 19 from the IMAGEN study, all from Europe. **Measurements.** Metrics of network segregation (modularity, clustering coefficient, and local efficiency) and integration (average shortest path length and global efficiency). **Findings.** The younger AD adults had lower network segregation and higher integration relative to non-dependent controls. Compared with controls, the hazardous drinkers at age 19 showed lower modularity (Area-under-the-curve [AUC] difference = -0.0142, confidence interval [CI] 95% [-0.1333, 0.0092]; p-value = 0.017), clustering coefficient (AUC difference = -0.0164 CI 95% [-0.1456, 0.0043], p-value = 0.008), and local efficiency (AUC difference = -0.0141 CI 95% [-0.0097, 0.0034], p-value = 0.010), as well as lower average shortest path length (AUC difference = -0.0405 CI 95% [-0.0392, 0.0096]; p-value = 0.021) and higher global efficiency (AUC difference = 0.0044 CI 95% [-0.0011, 0.0043]; p-value = 0.023). The same pattern was present at age 14 with lower clustering coefficient (AUC difference = -0.0131 CI 95% [-0.1304, 0.0033]; p-value = 0.024), lower average shortest path length (AUC difference = -0.0362 CI 95% [-0.0334, 0.0118]; p-value = 0.019), and higher global efficiency (AUC difference = 0.0035 CI 95% [-0.0011, 0.0038]; p-value = 0.048). **Conclusions.** Cross-sectional analyses indicate a specific structural covariance network profile is an early marker of alcohol dependence in adults. Similar effects in a cohort of heavy drinking adolescents, observed both at age 19 and prior to substantial alcohol exposure at age 14, suggest that this pattern may be a pre-existing risk factor for problematic drinking.

1. Introduction

Alcohol Dependence (AD) is characterized by persistent and compulsive alcohol use despite negative health consequences (1). Alcohol use entails an enormous burden for society and is a leading cause of preventable mortality worldwide (2). AD has been associated with lower grey matter volume across widespread regions of the brain and especially within prefrontal cortex and brain areas related to reward processing (3–5). The extent to which these effects arise from exposure due to consumption or reflect pre-existing differences which contribute to the development of AD remains unclear. Alcohol use initiates during adolescence (6), and early onset increases the risk for later problematic patterns of consumption including dependence (7). There is some evidence that alcohol use may disrupt brain maturation (8,9). While some studies have found regional grey matter differences in alcohol-naïve adolescents at risk for AD (10,11) others have found changes following exposure (12). The specifics regarding interactions between alcohol use and the brain in terms of pre-existing risk factors, age, and duration/quantity of use still require substantial clarification.

The study of structural covariance networks (SCN) provides an assessment of brain organization. Similar to functional connectivity, SCN is defined by regional covariance of distinct brain features. In SCN these features are structural, such as grey matter volume or cortical thickness. SCN detects networks that are partially consistent with those identified by functional and diffusion-based MRI (13). The presence of correlated brain features suggests synchronized maturation due to shared plastic or trophic influences. Evidence from neurodegenerative studies hints that network disturbances precede global grey matter decline, for example, in frontotemporal dementia (14), Parkinson's disease (15), and mild cognitive impairment (16). Network differences have also been reported in dependence on alcohol and other substances (17–19). Remarkably, network alterations were found in alcohol-naïve adolescents at greater risk for AD (20), which suggests these effects predate exposure and may represent a risk factor. However, such evidence comes from resting state fMRI studies and no work has reported such effects using SCN to date.

To summarize SCN features, we use graph theory which offers powerful and yet simple metrics to describe the relations within a network that is represented as a collection of nodes (e.g., brain regions) and edges (e.g., correlations). We explored group-level differences in

cortical thickness and graph theory metrics derived from SCN in two large samples. A cross-sectional dataset of adults with AD and non-dependent adult controls curated by the ENIGMA-Addiction consortium (https://www.enigmaaddiction.com), and a longitudinal adolescent cohort collected at ages 14 and 19 by the IMAGEN project (https://imagen-europe.com). We first examined whether the relationship between AD and cortical thickness in the adult sample was age dependent. Next, we explored the same adult sample for group differences in SCN metrics, assessing if these too were related to age. Then, turning to the adolescent sample, we tested whether cortical thickness and SCN properties were related to hazardous drinking patterns at age 19. Finally, we examined, retrospectively, if similar findings were present in the same sample at age 14 before substantial alcohol use.

2. Methods

2.1. Adult sample

A total of 1,724 participants (745 with AD and 979 non-dependent controls) ranging from 18 to 56 years old were included from 24 studies contributing to the ENIGMA-Addiction consortium. All procedures were in accordance with the Declaration of Helsinki. A variety of instruments were used to diagnose AD based on the DSM-IV criteria (see Table SM1 in the supplementary material). Participants with a history of neurological disease or contraindications for MRI were excluded. Additionally, individuals with AD were excluded for any other axis I disorder (i.e., including dependence to other substances) other than mood or anxiety.

Structural T1-weighted images were prepared using FreeSurfer (v.5.3) (21,22) through CBRAIN (www.computecanada.ca), a network of high-performance computing facilities in Canada (23). ENIGMA quality control protocols were followed (http://enigma.ini.usc.edu/protocols/imaging-protocols). Additional visual inspection was performed at the University of Vermont on random subsamples from each site to confirm consistent quality across sites. Details on the scanner vendor and image acquisition protocols are presented in the supplementary materials (Table SM1). Average cortical thickness was extracted from 68 regions of interest (ROIs) parcellated according to the Desikan-Killiany atlas (24). Inter-site scanner effects were removed with *ComBat* (25). This method allows one to

eliminate unwanted non-biological sources of variation from the data (i.e., scanner effects) while preserving relevant information such as age, sex, and group within a Bayesian framework. For a more detailed explanation please see Fortin et al. (2018).

2.1.1. Age windows

SCN exploits inter-individual variance in thickness to derive estimates of covariance at the group-level (see below). Consequently, in order to generate groups of AD and control participants for comparisons across different ages, the dataset was analyzed using a sliding window approach. The 6-year wide age windows started at age 18 and increased in steps of one year (i.e., 18-24, 19-25, 20-26… 50-56). The cut-off was set at age 56 due to limited numbers of individuals above this age. A 6-year window was selected as it maximized the numbers of individuals per window (100 on average) and ensured similar numbers of participants in each window while being reasonably narrow to detect age-related differences. We attempted to match AD and non-dependent groups for age and sex (ratio 1:1) at all windows using a nearest neighbor algorithm from the *MatchIt* package (26).

2.2. Adolescent sample

A sample of 1,068 adolescents was drawn from IMAGEN, a multi-site project which acquired longitudinal data at ages 14 (baseline) and 19 (follow-up) at eight European imaging centers. Non-siblings with MRI data available at baseline and follow-up were included. Missing age at follow-up from 112 participants was imputed with the average difference in years between baseline and follow-up (i.e., 4.64 years). The AUDIT was used to assess problematic alcohol use. AUDIT total scores equal to or greater than 8 indicate hazardous drinking (27). Participants surpassing this threshold at follow-up were classified as hazardous drinkers. Those who did not meet this cut-off (i.e., 7 or less) at baseline and follow-up were considered controls. Groups were matched for age and sex with a ratio of two controls for each hazardous drinker (2:1). The final groups were composed of 594 controls and 297 hazardous drinkers.

Structural T1-weighted scans were collected at each site following ADNI protocols to minimize site effects (28) (https://github.com/imagen2/imagen_mri/tree/master/protocols).

Preparation of images and site-effect adjustments were the same as described for the adult ENIGMA-Addiction sample.

2.3. Network construction

With this approach, a single network is derived from a correlation matrix exploiting inter-individual variation generated by pooling subjects from a predetermined group. The thickness of each ROI represents a node, and the correlation between ROIs describes an edge. The strength of an edge illustrates within-group correlations in thickness across pairs of nodes. Edges are thresholded and binarized and, finally, graph metrics are derived at the group-level. In both the adult and adolescent samples, ROIs were residualized for mean global thickness using linear regressions. Age and sex were residualized in the adult sample where balancing groups for these features was not possible. Adjacency matrices were generated with Pearson's correlations among the residualized ROIs for each group and age window in the adult sample, and for each group and time-point (i.e., follow-up and baseline) in the adolescent sample. This step returned group-specific (i.e., 2 groups, 2 matrices) correlation matrices of 68 by 68 nodes with a maximum possible density of 2,278 edges. Matrices were proportionally thresholded along a wide range of densities to prevent differences arising from unequal-sized networks or arbitrary thresholds. Matrices spanned from D_{min} to 0.3 in increasing steps of 0.01. Here, D_{min} equaled the minimum density at which groups displayed at least one edge per node: This ensured comparisons were done on fully connected networks. Network construction and metric derivation were performed with the *brainGraph* package (29).

2.4. Graph theory metrics

Global SCN properties were summarized with a variety of graph theory metrics assessing network segregation and integration across all densities.

Metrics of segregation rely on short-range edges and capture how correlated adjacent nodes are in terms of cortical thickness, with higher scores reflecting higher correlations. Three metrics of segregation were used: clustering coefficient (*Cp*), modularity, and local efficiency

(E_{local}). *Cp* reflects the extent to which the neighbors of a node are each other's neighbors (30). That is, it represents whether nodes that are correlated in thickness to a certain node are also correlated with each other. Modularity exposes the degree to which same-module nodes are correlated in thickness with each other but not with other modules (31). E_{local} expresses the ability of a cluster to remain connected (correlated) after a node is removed (32). If low, it may suggest that the relationships in thickness within a cluster is reliant on too few nodes.

Metrics of integration reveal between-community correlations and depend on shortcuts, or long-distance paths, to bring distant nodes together. We used the average shortest path length (*Lp*) and global efficiency (E_{global}). *Lp* denotes the average of the shortest number of edges passed through to reach other nodes in the network. This shortest path length is first calculated for all pairs of nodes sequentially (i.e., the average shortest path from A to B, from A to C, …, from X to Z) and then averaged across all nodes. E_{global} is comparable to the inverse of *Lp* (i.e., 1/*Lp*) with the exception that it incorporates all paths among two nodes (i.e., not just the shortest path but the full set of paths between A and B). By capturing these parallel or redundant paths, E_{global} is often preferred for networks that contain disconnected nodes (30). Note that these edges are in the graph space and reflect correlations in cortical thicknesses between brain regions so do not represent anatomical connectivity. Lower *Lp* and higher E_{global} imply a greater presence of shorter paths and better integrated networks (30) and indicate that distant nodes are more correlated. See supplementary materials for more details on these metrics (see Methods SM3).

2.5. Statistical analyses

None of the analyses conducted in the current work were pre-registered and should be therefore considered exploratory.

2.5.1. Cortical thickness comparisons

First, we examined if the difference in cortical thickness between AD and non-dependent groups was age dependent. For this purpose, we conducted linear regression models in the

full ENIGMA-Addiction adult sample (n = 1,724) to predict global (mean) cortical thickness by including group, sex, and age, and their interactions. Next, we adopted the moving age window approach to map group age-related differences in both global and regional cortical thickness. Age and sex balance was assessed at every window with parametric tests (i.e., t-test, chi-square test). If groups were different, age and sex were included as covariates. Models included global or regional cortical thickness as the dependent variable and group as its main predictor. A false-discovery rate (FDR) correction was adopted to minimize type I errors in regional cortical thickness analyses (i.e., 68 ROI = 68 tests per age window, 33 age windows).

In the adolescent sample, linear regressions for global and regional cortical thickness were done separately for follow-up and baseline with group as the main predictor and as well corrected for multiple comparisons with FDR (i.e., 68 tests, 2 time-points). All analyses were done in R (30).

2.5.2. Graph theory metrics comparisons

For both the adult and adolescent samples, between-group differences in graph theory metrics (i.e., *Cp*, modularity, E_{local}, *Lp*, E_{global}) were addressed with two-sided permutation tests at each density. Non-parametric permutation testing was required since metrics were calculated on the group level (i.e., one value per group). Area under the curve (AUC) analyses were used to prevent results from depending on a single threshold. Individuals were randomly shuffled among groups 1,000 times and two-sided AUC tests performed. The observed AUC differences were compared with critical values based on the 95^{th} percentile of the distribution of permuted AUC differences. The level of significance was set at p-value < 0.05 uncorrected. These analyses were performed at every age window (n = 33) in the adult sample, and for follow-up and baseline in the adolescent sample. Supplementary tests involved a subset of hazardous drinkers (n = 110) and controls (n = 220) with no alcohol use at baseline (AUDIT = 0) to investigate if any observed effect could be disentangled from exposure.

2.5.3. Behavioral and cognitive tests

To better characterize the phenotype of each group, we examined group differences on the DAWBA externalizing problems scale, the impulsivity scale from the Temperament and Character Inventory (TCI), as well as the risk-taking score from the Cambridge Gambling Task (CGT). Groups were compared in a series of cross-sectional linear mixed models adjusting for fixed (i.e., age and sex) and random effects (i.e., site). Because of their exploratory nature, the significance level for these tests was Bonferroni-adjusted and set at p-value < 0.008 (3 tests per 2 visits: 0.05/6 = 0.008).

3. Results

A summary of sociodemographic characteristics of the adult ENIGMA-Addiction and adolescent IMAGEN samples is available in Table 1.

3.1. Cortical thickness results

In the adult sample, the AD group exhibited lower global cortical thickness compared to the non-dependent group (t_{1716} = -4.42, p-value < 0.001). Whereas the group x sex interaction was not significant (t_{1716} = -0.52, p-value = 0.606), the group x age interaction was significant (t_{1716} = -3.20, p-value = 0.001). The AD group had a steeper age-related slope (r = -0.32) than non-dependent controls (r = -0.24) (see Figure 1). The main effect of sex (t_{1716} = -0.60, p-value = 0.547) and its interaction with age (t_{1716} = 0.75, p-value = 0.454) were not significant.

Contrasts performed at each age window showed groups differed on global cortical thickness at age window 25-31 and in each subsequent age window (see Figure 2). Also, ROI-level contrasts revealed that the number of regions with a significant difference in thickness increased in the older age windows (e.g., from 4 ROIs at age window 18-24 to 54 ROIs at age window 41-47). Further ROI results are provided in the supplementary materials (Figure SM2; plots done with the *ggseg* package (31)). Table 2 presents demographic summaries at each age window.

A group difference in cortical thickness was not observed in the adolescent sample at either baseline or follow-up.

3.3. Structural covariance results

In the adult sample, the AD group exhibited significantly lower modularity, *Cp,* and E_{local} relative to the non-dependent group in the younger age windows, consistent with lower segregation. Whereas modularity effects were present at the 18-24 age window only, *Cp* and E_{local} effects were significant in all windows starting at 18-24 until age window 26-32 (see Figure 2). A single effect emerged at age window 41-47 but only for *Cp*. The AD group had significantly higher E_{global} in age window 19-25. This group showed lower *Lp* and higher E_{global} from age windows 21-27 to 24-30, suggesting greater integration. The AD group showed higher E_{global} at age window 26-32. At age window 41-47, this group had lower *Lp* and greater E_{global} (note: all analyses were repeated using different age window solutions [e.g., 5-year, 7-year, 8-year, 9-year, and 10-year wide windows] and results remained significant in the younger AD; results not shown). The observed differences and confidence intervals (CI) are available in the supplementary materials (see SM4).

In the adolescent sample, significant effects were found at follow-up for all graph theory metrics. Similar to the early age windows in the adult AD group, the adolescent hazardous drinking group exhibited lower modularity (AUC difference = -0.0142, CI 95% [-0.1333, 0.0092]; p-value = 0.017), *Cp* (AUC = -0.0164, CI 95% [-0.1456, 0.0043]; p-value = 0.008), and E_{local} (AUC difference = -0.0141, CI 95% [-0.0097, 0.0034]; p-value = 0.010) compared to controls (see Figure 3). Likewise, adolescent hazardous drinkers also presented lower *Lp* (AUC difference = -0.0405, CI 95% [-0.0392, 0.0096]; p-value = 0.021) and greater E_{global} (AUC difference = 0.0044, CI 95% [-0.0011, 0.0043]; p-value = 0.023). A number of effects were observed at baseline mimicking those observed at follow-up and at the early age windows in the adult sample. At baseline (i.e., age 14), and prior to substantial alcohol exposure, the future hazardous drinking group had lower *Cp* (AUC difference = -0.0131, CI 95% [-0.1304, 0.0033]; p-value = 0.024), lower *Lp* (AUC difference = -0.0362, CI 95% [-0.0334, 0.0118]; p-value = 0.019), and higher E_{global} (AUC difference = 0.0035, CI 95% [-0.0011, 0.0038]; p-value = 0.048). A subset of the hazardous drinking adolescents who were alcohol-naïve at baseline

(i.e., AUDIT = 0) showed a similar pattern to the larger group at follow-up although the effects were not significant (see Figure 3).

3.4. Behavioral and cognitive results

At age 19, the hazardous drinking group exhibited higher externalizing symptoms ($t_{747.58}$ = 3.94, p-value < 0.001), impulsivity ($t_{631.87}$ = 4.83, p-value < 0.001) and risk-taking scores ($t_{868.93}$ = 3.61, p-value < 0.001) compared to the control group. Similarly, at age 14, the (future) hazardous drinking group scored higher on externalizing symptoms ($t_{825.09}$ = 2.87, p-value = 0.004) and impulsivity (t_{756} = 2.71, p-value = 0.007). Risk-taking results did not survive Bonferroni-adjustments ($t_{605.12}$ = 2.12, p-value = 0.035).

4. Discussion

In a large adult cross-sectional sample, we found that the difference in global cortical thickness between AD and non-dependent groups was influenced by age, being greater in older individuals. The sliding age window analysis identified an initial significant group difference in global cortical thickness in the 25-31 age window and in all the older age windows. With regard to SCN, the AD group consistently presented lower segregation and higher integration of SCN compared to non-dependent controls in the younger but not the older age windows, an opposite pattern to what was observed with the average cortical thickness. We found similar SCN effects in an independent sample of adolescents with no cortical thickness differences in hazardous drinkers at age 19. Most notably, SCN differences were observed in the same adolescents five years earlier who, at age 14, had little to no lifetime alcohol exposure. Taken together, results indicate that SCN effects are related to alcohol drinking (i.e., alcohol dependence or hazardous drinking) in the absence of cortical thickness differences.

4.1. Alcohol and Brain Volume

Initiation of alcohol use typically occurs during adolescence (6), and early onset increases the risk for later problematic patterns of use including dependence (7). Youths initiating alcohol

use by age 14 or earlier are five times more likely to be diagnosed as AD later in life than those who started at age 21 or later. From age 14 onwards, each year by which onset of drinking is delayed is followed by a 14% drop in the risk for lifetime dependence (32). Onset of AD peaks in the early 20s (33), with most cases (94.1%) being diagnosed before age 25 (34). With regard to the brain, older individuals with AD show more regional differences in cortical volume compared to non-dependent controls and to younger individuals with AD (35–37). The effects of age and chronic alcohol use on the brain have been confirmed in animal models (38). Sustained alcohol exposure reduces brain-derived neurotrophic factor and nerve-growth factor release, triggers oxidative stress and glutamate excitotoxicity, and disturbs mitochondrial function due to the accumulation of toxic metabolites (12). Some of these factors are related to the etiology of neurodegenerative disease (39). Whilst the cross-sectional nature of the adult sample warrants caution, differences in cortical thickness as a function of age quite plausibly reflect the cumulative effect of exposure. However, it is equally possible that older brains are more susceptible to the alcohol neurotoxicity or that the AD duration is influenced by pre-existing grey matter differences.

4.3. Alcohol Use and Structural Covariance

Consistent with the present findings, resting-state fMRI studies have reported lower network segregation in alcohol-naïve adolescents at risk of AD (18) and AD severity in adults (20). Lower segregation has also been found in cocaine and heroin dependence (17,19), and internet-gaming disorder (40). In contrast, the literature is less consistent as to differences in network integration in both AD and other addictions (17–20,40). In the present findings, segregation and integration effects appeared at age windows 18-24 and 21-27 and were not observed in age window 26-32 or older. Although we cannot confirm with cross-sectional data that SCN differences predict grey matter decay as in neurodegenerative work, we speculate that the absence of SCN differences at later windows could be related to the onset of cortical thickness effects that obscure SCN effects.

We extended the investigation to an adolescent longitudinal dataset to explore if SCN differences could be observed in those who do not have AD but are showing patterns of hazardous drinking. The adolescent sample replicated the young adult AD group's SCN findings, including the absence of cortical thickness differences relative to controls. At follow-

up, the hazardous drinking group had lower segregation (i.e., lower modularity, *Cp* and E_{local}) and higher integration (i.e., lower *Lp* and higher E_{global}) than controls. At baseline, the (future) hazardous drinking group showed lower segregation (i.e., lower *Cp*) and higher integration (i.e., lower *Lp*, higher E_{global}) than controls. Of note, most of the individuals from this group had below threshold scores (AUDIT < 8), and 37% had reported no alcohol use (AUDIT = 0) at baseline. While supplementary tests on this alcohol-naïve subset (i.e., 37%, n = 110) showed similar effects to the larger group at age 19, null results were found at baseline. Nevertheless, this analysis drastically reduced the sample size and thus chances of type II error cannot be dismissed.

As graph theory metrics derived from SCN describe the degree of synchronized maturation across nodes (41–43), lower segregation hints at de-synchronization among adjacent nodes in the young AD and the adolescent hazardous drinking groups. By contrast, higher integration means greater synchronization with nodes that belong to other communities. In other words, brain regions are showing atypical similarity in thicknesses to other regions that are distant in the alcohol drinking groups. Poor segregation and higher integration have previously been related to other psychiatric and neurological conditions (44), including dependence on alcohol and other substances (16–18). Typically, segregation peaks by late adolescence and young adulthood likely reflecting functional specialization among cortical regions (44,45). Therefore, we speculate that our results suggest a protracted cortical maturation in the alcohol drinking groups (13,42,47). Asynchronous cortical growth has previously been related to poor decision-making and self-regulation and to elevated reward-seeking behaviors (47,48). Delayed cortical growth has been associated with inattention (49) and anxious/depression symptoms (50) as well. It has been proposed that disturbed cortical growth renders youth vulnerable to risky behaviors such as early alcohol drinking (48,51). In Holla et al. (2017), delayed maturation of functional networks in adolescents at greater risk for alcohol dependence was associated with more externalizing problems. Externalizing problems suggest failures in self-regulation also resulting a risk factor for alcohol use (50). We have found that the hazardous drinking group presented higher externalizing symptom severity scores, were more impulsive, and took more risky decisions in a gambling task at ages 14 and 19. Additionally, if the SCN results are an indicator of delayed cortical growth, then the absence of SCN effects after the age window 26-32 in AD adults could align with the end of

the delayed developmental period. That is, the group differences in SCN may disappear because the relevant maturational processes are complete in both the AD and non-dependent controls. For instance, the *Cp* trajectories in Figure 1 show that the peak in the AD group (age window 28-34) appears delayed as to the peak in the control group (age window 23-29). An alternative possibility is that SCN differences persist but are obscured by the widespread cortical thinning associated with adult AD.

To summarize, the younger AD group exhibited lower segregation and higher integration in the absence of global differences in cortical thickness relative to the control group. The very same pattern was found at age 19 in adolescents with hazardous drinking behavior. This profile was again detected in the same group five years earlier prior to substantial alcohol exposure. Overall, we hypothesize that the SCN profile might reflect the delayed growth of cortico-cortical networks central to the development of functional specializations and related to the successful regulation of reward-related processes. We have also found behavioral signs that suggest delays in cortical maturation. Impaired self-regulation during adolescence (i.e., higher impulsivity and risk-taking) increases the likelihood of engaging in problematic behaviors such as alcohol use (47,48,51). Still, with the current design and approach, we cannot confirm whether SCN differences constitute a risk factor for alcohol use or dependence nor if these were independent from exposure; similar but not significant effects were found in a sample of alcohol-naïve individuals at age 14, which we attribute to loses in statistical power. However, our analyses provide evidence of a promising brain marker for AD in young adults and for heavy alcohol use at age 19. We offer a retrospective prediction in which a known outcome (i.e., heavy drinking at age 19) is predated by SCN changes at age 14 before any substantial alcohol use. Despite the exploratory nature and methodological limitations, the current study brings intriguing new hypotheses about potential brain markers for future alcohol use.

The current study was limited by several factors. First, alcohol use duration was not measured at many of the ENIGMA-Addiction sites, so it was not possible to disentangle the potential effects of duration and age. Many studies have reported that age and alcohol use duration are highly collinear especially among heavy drinkers (36). Despite dependence on other substances and the presence of other psychiatric disorders being considered reasons for

exclusion, we cannot discard other factors such as recreational use of other drugs, anxiety and depression symptoms, or lower education and socioeconomic status partially explaining the results. Age distribution was skewed in the adult sample which required the analyses to go no further than age 56. More notably, the cross-sectional nature of the adult sample restricts the conclusions that we can draw regarding SCN effects preceding, or indeed being causally related to cortical thickness alterations within an AD individual. Moreover, contrasts for both the adult and adolescent samples were performed at the group-level as the SCN approach exploited inter-individual variation so did not provide individual-level metrics. Due to insufficient numbers of female individuals (32% in the AD group), relevant questions on sex differences were left unexplored. Last, and to the best of our knowledge, this is the first study using SCN metrics and alcohol and hence the current work has a strong exploratory component.

In conclusion, based on two of the largest datasets with neuroimaging data and relevant alcohol phenotypes, young adults with alcohol dependence showed a specific pattern of SCN differences. This SCN profile was replicated in adolescents identified as hazardous drinkers at age 19 and prior to substantial exposure to alcohol at age 14. SCN differences were found in the absence of global differences in cortical thickness. Lower segregation and higher integration were found in cortical networks which may indicate disruptions in cortico-cortical growth. Further work should address whether such effects represent an early marker for future alcohol use and dependence.

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References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association; 2013.
2. Griswold MG, Fullman N, Hawley C, Arian N, Zimsen SRM, Tymeson HD, et al. Alcohol use and burden for 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2018;392(10152):1015–35.
3. Fritz M, Klawonn AM, Zahr NM. Neuroimaging in alcohol use disorder: From mouse to man. Journal of Neuroscience Research. 2019;(May).
4. Morris VL, Owens MM, Syan SK, Petker TD, Sweet LH, Oshri A, et al. Associations Between Drinking and Cortical Thickness in Younger Adult Drinkers: Findings From the Human Connectome Project. Alcoholism: Clinical and Experimental Research. 2019 Sep;43(9):1918–27.
5. Mackey S, Allgaier N, Chaarani B, Spechler P, Orr C, Bunn J, et al. Mega-analysis of gray matter volume in substance dependence: General and substance-specific regional effects. American Journal of Psychiatry. 2019;176(2):119–28.
6. Petit G, Kornreich C, Verbanck P, Cimochowska A, Campanella S. Why is adolescence a key period of alcohol initiation and who is prone to develop long-term problem use?: A review of current available data. Socioaffective Neuroscience & Psychology [Internet]. 2013 Jan 11;3(1):21890. Available from: https://www.tandfonline.com/doi/full/10.3402/snp.v3i0.21890
7. Hingson RW, Heeren T, Winter MR. Age at Drinking Onset and Alcohol Dependence. Archives of Pediatrics & Adolescent Medicine [Internet]. 2006 Jul 1;160(7):739. Available from: http://archpedi.jamanetwork.com/article.aspx?doi=10.1001/archpedi.160.7.739
8. Crews FT, Vetreno RP, Broadwater MA, Robinson DL. Adolescent Alcohol Exposure Persistently Impacts Adult Neurobiology and Behavior. Morrow LA, editor. Pharmacological Reviews. 2016 Oct 27;68(4):1074–109.
9. Ruan H, Zhou Y, Luo Q, Robert GH, Desrivières S, Quinlan EB, et al. Adolescent binge drinking disrupts normal trajectories of brain functional organization and personality maturation. NeuroImage: Clinical. 2019;22:101804.
10. Benegal V, Antony G, Venkatasubramanian G, Jayakumar PN. Gray matter volume abnormalities and externalizing symptoms in subjects at high risk for alcohol dependence. Addiction Biology. 2007 Mar;12(1):122–32.
11. Henderson KE, Vaidya JG, Kramer JR, Kuperman S, Langbehn DR, O'Leary DS. Cortical Thickness in Adolescents with a Family History of Alcohol Use Disorder. Alcoholism: Clinical and Experimental Research. 2018 Jan;42(1):89–99.
12. Brust JCM. Ethanol and cognition: Indirect effects, neurotoxicity and neuroprotection: A review. International Journal of Environmental Research and Public Health. 2010;7(4):1540–57.
13. Evans AC. Networks of anatomical covariance. NeuroImage. 2013 Oct;80:489–504.

14. Brown JA, Deng J, Neuhaus J, Sible IJ, Sias AC, Lee SE, et al. Patient-Tailored, Connectivity-Based Forecasts of Spreading Brain Atrophy. Neuron. 2019;104(5):856-868.e5.
15. Yau Y, Zeighami Y, Baker TE, Larcher K, Vainik U, Dadar M, et al. Network connectivity determines cortical thinning in early Parkinson's disease progression. Nature Communications. 2018;9(1):1–10.
16. Nir TM, Jahanshad N, Toga AW, Bernstein MA, Jack CR, Weiner MW, et al. Connectivity network measures predict volumetric atrophy in mild cognitive impairment. Neurobiology of Aging. 2015 Jan;36(1):S113–20.
17. Wang Z, Suh J, Li Z, Li Y, Franklin T, O'Brien C, et al. A hyper-connected but less efficient small-world network in the substance-dependent brain. Drug and Alcohol Dependence. 2015 Jul;152(1):102–8.
18. Holla B, Panda R, Venkatasubramanian G, Biswal B, Bharath RD, Benegal V. Disrupted resting brain graph measures in individuals at high risk for alcoholism. Psychiatry Research - Neuroimaging. 2017;265(May):54–64.
19. Jiang G, Wen X, Qiu Y, Zhang R, Wang J, Li M, et al. Disrupted Topological Organization in Whole-Brain Functional Networks of Heroin-Dependent Individuals: A Resting-State fMRI Study. Biagini G, editor. PLoS ONE. 2013 Dec 17;8(12):e82715.
20. Sjoerds Z, Stufflebeam SM, Veltman DJ, Van den Brink W, Penninx BWJH, Douw L. Loss of brain graph network efficiency in alcohol dependence. Addiction Biology. 2017;22(2):523–34.
21. Fischl. Whole Brain Segmentation: Automated Labeling of Neuroanatomical Structures in the Human Brain. Neuron. 2002;33:341–55.
22. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proceedings of the National Academy of Sciences. 2000;97(20):11050–5.
23. Sherif T, Rioux P, Rousseau M-E, Kassis N, Beck N, Adalat R, et al. CBRAIN: a web-based, distributed computing platform for collaborative neuroimaging research. Frontiers in Neuroinformatics. 2014 May 21;8.
24. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage. 2006;31(3):968–80.
25. Fortin J-P, Cullen N, Sheline YI, Taylor WD, Aselcioglu I, Cook PA, et al. Harmonization of cortical thickness measurements across scanners and sites. NeuroImage. 2018 Feb;167:104–20.
26. Ho DE, King G, Stuart EA, Imai K. MatchIt : Nonparametric Preprocessing for. Journal Of Statistical Software. 2011;42(8):1–28.
27. Saunders JB, Aasland OG, Babor TF, De la Fuente JR, Gran M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption-II. Addiction. 1993 Jun;88(6):791–804.
28. Schumann G, Loth E, Banaschewski T, Barbot A, Barker G, Buchel C, et al. The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. Molecular psychiatry. 2010 Dec;15(12):1128–39.
29. Watson CG, Stopp C, Newburger JW, Rivkin MJ. Graph theory analysis of cortical thickness networks in adolescents with d-transposition of the great arteries. Brain and Behavior. 2018 Feb;8(2):e00834.

30. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria; 2018.
31. Mowinckel AM, Vidal-Piñeiro D. Visualisation of Brain Statistics with R-packages ggseg and ggseg3d. 2019 Dec 17;
32. Grant BF, Dawson DA. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: Results from the national longitudinal alcohol epidemiologic survey. Journal of Substance Abuse. 1997;9(1):103–10.
33. Olsson CA, Romaniuk H, Salinger J, Staiger PK, Bonomo Y, Hulbert C, et al. Drinking patterns of adolescents who develop alcohol use disorders: results from the Victorian Adolescent Health Cohort Study. BMJ Open. 2016 Feb 11;6(2):e010455.
34. Wetterling T, Veltrup C, John U, Driessen M. Late onset alcoholism. European Psychiatry. 2003 May 16;18(3):112–8.
35. Pfefferbaum A, Zahr NM, Sassoon SA, Kwon D, Pohl KM, Sullivan E V. Accelerated and Premature Aging Characterizing Regional Cortical Volume Loss in Human Immunodeficiency Virus Infection: Contributions From Alcohol, Substance Use, and Hepatitis C Coinfection. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2018 Oct;3(10):844–59.
36. Fein G, Sclafani V, Cardenas VA, Goldmann H, Tolou-Shams M, Meyerhoff DJ. Cortical Gray Matter Loss in Treatment-Naive Alcohol Dependent Individuals. Alcoholism: Clinical and Experimental Research. 2006 Apr 1;26(4):558–64.
37. Sullivan E V., Zahr NM, Sassoon SA, Thompson WK, Kwon D, Pohl KM, et al. The Role of Aging, Drug Dependence, and Hepatitis C Comorbidity in Alcoholism Cortical Compromise. JAMA Psychiatry. 2018 May 1;75(5):474.
38. Zahr NM, Sullivan E V., Pohl KM, Pfefferbaum A. Age differences in brain structural and metabolic responses to binge ethanol exposure in fisher 344 rats. Neuropsychopharmacology. 2020 Jun 24;
39. Bossy-Wetzel E, Schwarzenbacher R, Lipton SA. Molecular pathways to neurodegeneration. Nature Medicine. 2004 Jul 1;10(S7):S2–9.
40. Zhai J, Luo L, Qiu L, Kang Y, Liu B, Yu D, et al. The topological organization of white matter network in internet gaming disorder individuals. Brain Imaging and Behavior. 2017 Dec 4;11(6):1769–78.
41. Alexander-Bloch A, Giedd JN, Bullmore E. Imaging structural co-variance between human brain regions. Nature Reviews Neuroscience. 2013 May 27;14(5):322–36.
42. Griffiths KR, Grieve SM, Kohn MR, Clarke S, Williams LM, Korgaonkar MS. Altered gray matter organization in children and adolescents with ADHD: a structural covariance connectome study. Translational psychiatry. 2016;6(11):e947.
43. Jirsaraie RJ, Kaczkurkin AN, Rush S, Piiwia K, Adebimpe A, Bassett DS, et al. Accelerated cortical thinning within structural brain networks is associated with irritability in youth. Neuropsychopharmacology. 2019;44(13):2254–62.
44. Liao X, Vasilakos A V., He Y. Small-world human brain networks: Perspectives and challenges. Neuroscience and Biobehavioral Reviews. 2017;77(January):286–300.
45. Vijayakumar N, Ball G, Seal ML, Mundy L, Whittle S, Silk T. The development of structural covariance networks during the transition from childhood to adolescence. Scientific Reports. 2021 Dec 4;11(1):9451.
46. Hagmann P, Sporns O, Madan N, Cammoun L, Pienaar R, Wedeen VJ, et al. White matter maturation reshapes structural connectivity in the late developing human

brain. Proceedings of the National Academy of Sciences. 2010 Nov 2;107(44):19067–72.
47. Geier CF. Adolescent cognitive control and reward processing: Implications for risk taking and substance use. Hormones and Behavior. 2013 Jul;64(2).
48. Dayan J, Bernard A, Olliac B, Mailhes AS, Kermarrec S. Adolescent brain development, risk-taking and vulnerability to addiction. Journal of Physiology Paris [Internet]. 2010;104(5–6):279–86. Available from: http://dx.doi.org/10.1016/j.jphysparis.2010.08.007
49. Ducharme S, Hudziak JJ, Botteron KN, Albaugh MD, Nguyen TV, Karama S, et al. Decreased regional cortical thickness and thinning rate are associated with inattention symptoms in healthy children. Journal of the American Academy of Child and Adolescent Psychiatry. 2012;51(1).
50. Albaugh MD, Nguyen TV, Ducharme S, Collins DL, Botteron KN, D'Alberto N, et al. Age-related volumetric change of limbic structures and subclinical anxious/depressed symptomatology in typically developing children and adolescents. Biological Psychology. 2017 Mar 1;124:133–40.
51. Bava S, Tapert SF. Adolescent Brain Development and the Risk for Alcohol and Other Drug Problems. Neuropsychology Review. 2010 Dec 19;20(4).
52. Kuperman S, Chan G, Kramer JR, Bierut L, Bucholz KK, Fox L, et al. Relationship of Age of First Drink to Child Behavioral Problems and Family Psychopathology. Alcoholism: Clinical & Experimental Research. 2005 Oct;29(10):1869–76.

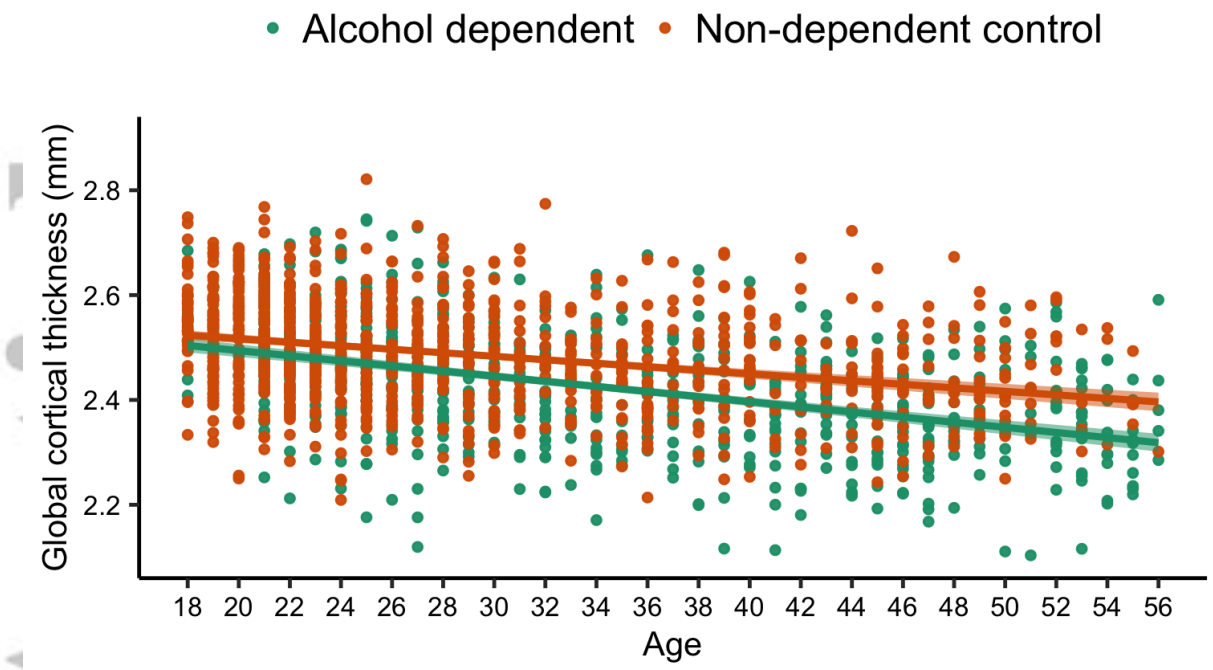

Figure 1 – Global cortical thickness and age interaction between groups.

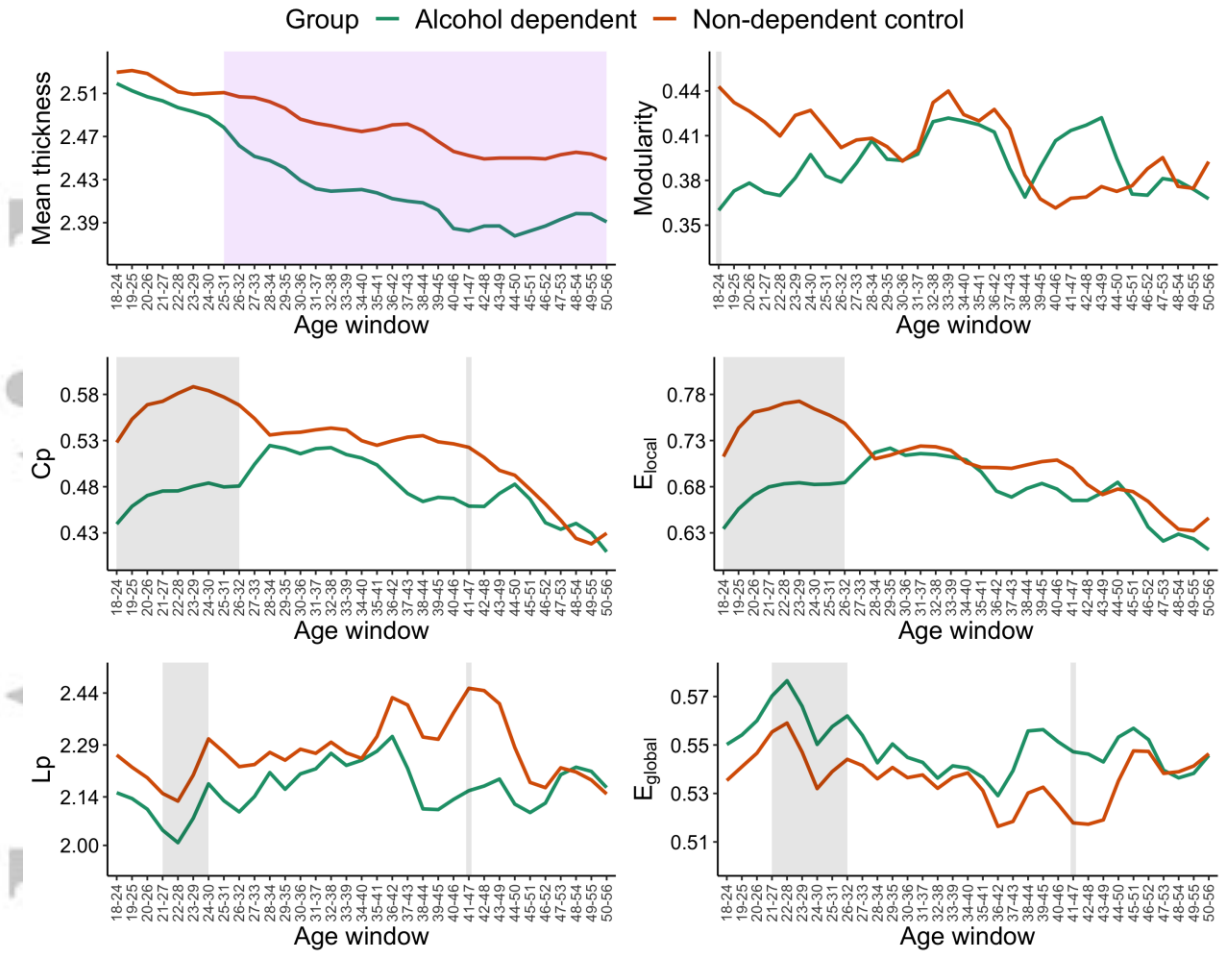

Figure 2 – Global cortical thickness and graph theory metrics plotted as a function of age using age windows for the ENIGMA-Addiction dataset. Shaded areas represent statistically significant differences ($p < 0.05$) between groups.

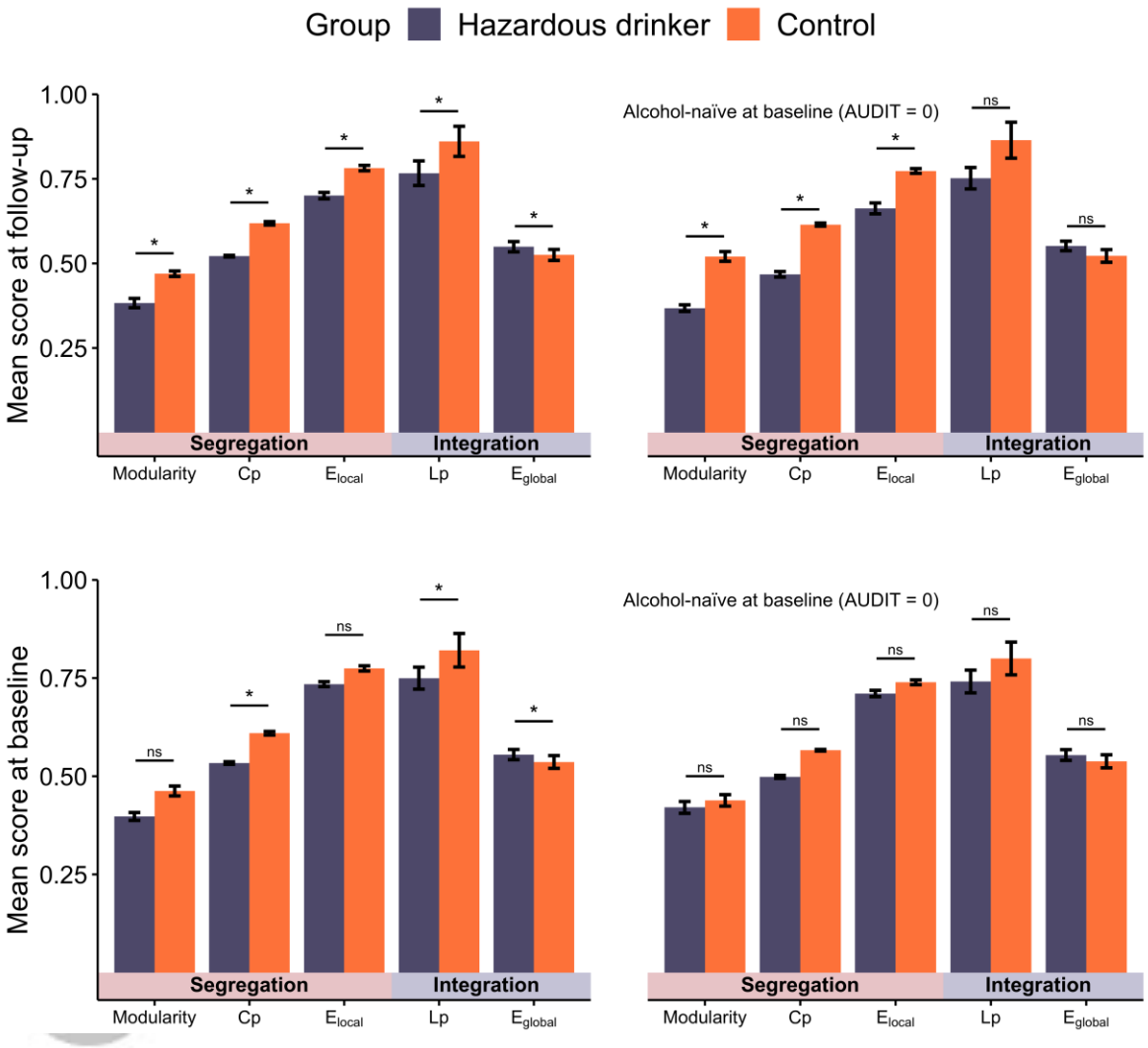

Figure 3 – Average score of graph theory metrics across densities at follow-up (first row) and baseline (second row). Right-column barplots represent analyses done in a subset of participants that were alcohol-naïve at baseline. Error bars depict the standard error for each measure across densities. Lp values were log-scaled to fit the rest of the variables. * $p < 0.05$, n.s., non-significant.

Table 1 – Demographics for Adults and Adolescents (mean ± standard deviation, or frequency).

		N	Age	Females	AUDIT total
Adults	Alcohol dependent	745	33.9 ± 10.3	239	-
	Non-dependent	979	28.9 ± 9.58	406	-
Follow-up adolescents	Hazardous drinkers	297	19.1 ± 0.74	126	11.6 ± 3.87
	Controls	594	19.1 ± 0.72	255	3.63 ± 2.12
Baseline adolescents	Hazardous drinkers	297	14.4 ± 0.36	126	1.95 ± 2.58
	Controls	594	14.4 ± 0.41	255	0.84 ± 1.41

Table 2 – Demographics for Adults age windows (mean ± standard deviation, or frequency; *p < 0.05).

Age window		Alcohol dependent	Non-dependent	Statistic (t/X^2)
18-24	N	182	182	-
	Age	22.3 ± 1.43	22.3 ± 1.43	0
	Female	75	79	0.10
19-25	N	209	209	-
	Age	22.9 ± 1.44	22.9 ± 1.44	0
	Female	84	88	0.09
20-26	N	243	243	-
	Age	23.4 ± 1.69	23.4 ± 1.70	-0.13
	Female	94	98	0.08
21-27	N	269	269	-
	Age	23.7 ± 1.94	23.7 ± 1.91	0.18
	Female	103	103	0
22-28	N	258	258	-
	Age	24.7 ± 1.98	24.7 ± 1.99	0.18
	Female	100	99	0
23-29	N	232	232	-
	Age	25.6 ± 1.92	25.6 ± 1.92	-0.16
	Female	90	90	0
24-30	N	217	217	-
	Age	26.5 ± 2.01	26.6 ± 2.00	-0.17
	Female	81	81	0
25-31	N	188	188	-
	Age	27.6 ± 1.96	27.6 ± 1.95	0
	Female	65	65	0
26-32	N	178	178	-
	Age	28.6 ± 2.05	28.5 ± 1.92	0.53
	Female	62	63	0
27-33	N	151	151	-
	Age	29.5 ± 1.90	29.5 ± 1.93	-0.03
	Female	52	52	0
28-34	N	147	147	-
	Age	30.7 ± 2.08	30.6 ± 2.00	0.31
	Female	50	57	0.53
29-35	N	132	132	-
	Age	31.9 ± 2.00	31.5 ± 2.03	1.47
	Female	37	37	0
30-36	N	130	130	-
	Age	32.8 ± 2.05	32.7 ± 2.17	0.23
	Female	39	44	0.28
31-37	N	121	121	-
	Age	33.9 ± 2.01	33.9 ± 1.99	-0.06
	Female	36	46	1.49
32-38	N	122	122	-
	Age	35.0 ± 2.07	35.0 ± 1.94	-0.22
	Female	36	44	0.91
33-39	N	113	113	-
	Age	36.1 ± 1.91	36.1 ± 1.91	0.03
	Female	31	34	0.09
34-40	N	120	120	-
	Age	36.8 ± 2.05	36.8 ± 1.95	-0.10
	Female	32	42	1.58
35-41	N	115	115	-
	Age	38.0 ± 2.02	37.8 ± 1.89	0.98

	Female	28	39	2.11
	N	111	111	-
36-42	Age	38.9 ± 1.96	38.6 ± 1.94	1.24
	Female	32	42	1.64
	N	95	95	-
37-43	Age	39.4 ± 1.75	39.6 ± 1.82	-0.65
	Female	30	34	0.21
	N	93	93	-
38-44	Age	40.3 ± 1.70	40.5 ± 1.99	-0.59
	Female	26	38	2.88
	N	96	96	-
39-45	Age	41.5 ± 1.67	41.9 ± 2.26	-1.96
	Female	22	44	**10.18***
	N	94	94	-
40-46	Age	43.7 ± 1.71	43.2 ± 2.21	1.66
	Female	27	38	2.35
	N	84	84	-
41-47	Age	45.2 ± 1.70	44.3 ± 1.85	**3.17***
	Female	32	35	0.10
	N	85	85	-
42-48	Age	44.4 ± 1.89	45.0 ± 1.81	-2.36
	Female	36	36	0
	N	88	88	-
43-49	Age	46.7 ± 1.52	46.0 ± 1.88	**2.43***
	Female	31	35	0.22
	N	92	92	-
44-50	Age	47.2 ± 1.57	46.8 ± 2.01	1.52
	Female	27	36	1.54
	N	88	88	-
45-51	Age	47.8 ± 1.64	47.5 ± 2.03	1.10
	Female	28	28	0
	N	74	74	-
46-52	Age	48.9 ± 2.12	48.5 ± 1.95	1.17
	Female	9	20	**4.29***
	N	62	62	-
47-53	Age	49.4 ± 2.05	49.6 ± 1.80	-0.51
	Female	0	16	**16.15***
	N	56	56	-
48-54	Age	50.0 ± 1.73	50.2 ± 1.76	-0.81
	Female	10	14	0.48
	N	52	52	-
49-55	Age	51.0 ± 1.43	51.1 ± 1.98	-0.23
	Female	13	13	0
	N	39	39	-
50-56	Age	51.5 ± 1.07	52.0 ± 1.87	-1.41
	Female	11	8	0.28