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Hierarchical associations of alcohol use disorder symptoms in late adolescence with markers during early adolescence

Simone Kühn[22,23*], Ph.D.; Nina Lisofsky[22], Ph.D.; Tobias Banaschewski M.D., Ph.D.[1]; Gareth Barker Ph.D.[2]; Arun L.W. Bokde Ph.D.[3]; Uli Bromberg Ph.D.[4]; Christian Büchel M.D.[4]; Rüdiger Brühl[12]; Erin Burke Quinlan, PhD[5]; Sylvane Desrivières Ph.D.[5]; Herta Flor Ph.D.[6,7]; Antoine Grigis Ph.D.[8]; Hugh Garavan Ph.D.[9]; Penny Gowland Ph.D.[10]; Andreas Heinz M.D., Ph.D.[11]; Bernd Ittermann Ph.D.[12]; Jean-Luc Martinot M.D., Ph.D.[13]; Marie-Laure Paillère Martinot M.D., Ph.D.[13,14]; Frauke Nees Ph.D.[1,6]; Dimitri Papadopoulos Orfanos Ph.D.[8]; Tomáš Paus M.D., Ph.D.[17]; Luise Poustka M.D.[18,19]; Juliane H. Fröhner Dipl.-Psych.[20]; Michael N. Smolka M.D.[20]; Henrik Walter M.D., Ph.D.[11]; Robert Whelan Ph.D.[21]; Gunter Schumann M.D.[5]; Jürgen Gallinat M.D. [23]; IMAGEN Consortium

[1]Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Square J5, 68159 Mannheim, Germany;

[2]Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom;

[3]Discipline of Psychiatry, School of Medicine and Trinity College Institute of Neuroscience, Trinity College Dublin, Ireland;

[4]University Medical Centre Hamburg-Eppendorf, House W34, 3.OG, Martinistr. 52, 20246, Hamburg, Germany;

[5]Medical Research Council - Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom;

[6]Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Square J5, Mannheim, Germany;

[7] Department of Psychology, School of Social Sciences, University of Mannheim, 68131 Mannheim, Germany;

[8] NeuroSpin, CEA, Université Paris-Saclay, F-91191 Gif-sur-Yvette, France;

[9]Departments of Psychiatry and Psychology, University of Vermont, 05405 Burlington, Vermont, USA;

[10]Sir Peter Mansfield Imaging Centre School of Physics and Astronomy, University of Nottingham, University Park, Nottingham, United Kingdom;

[11]Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité, Universitätsmedizin Berlin, Charitéplatz 1, Berlin, Germany;

[12]Physikalisch-Technische Bundesanstalt (PTB), Braunschweig and Berlin, Germany

[13]Institut National de la Santé et de la Recherche Médicale, INSERM Unit 1000 “Neuroimaging & Psychiatry”, University Paris Sud, University Paris Descartes - Sorbonne Paris Cité; and Maison de Solenn, Paris, France;

[14] AP-HP, Department of Adolescent Psychopathology and Medicine, Maison de Solenn, Cochin Hospital, Paris, France;

[17]Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital and Departments of Psychology and Psychiatry, University of Toronto, Toronto, Ontario, M6A 2E1, Canada

[18]Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Centre Göttingen, von-Siebold-Str. 5, 37075, Göttingen, Germany;

[19]Clinic for Child and Adolescent Psychiatry, Medical University of Vienna, Währinger Gürtel 18-20, 1090, Vienna, Austria;

[20]Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, Dresden, Germany;

[21]School of Psychology and Global Brain Health Institute, Trinity College Dublin, Ireland;

[22]Max Planck Institute for Human Development, Berlin, Germany;

[23] University Medical Center Hamburg-Eppendorf (UKE), Department of Psychiatry and Psychotherapy, Martinistrasse 52, 20246 Hamburg, Germany

*Correspondence concerning this article should be addressed to Simone Kühn, s.kuehn@uke.de , University Clinic Hamburg-Eppendorf

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Abstract

High adolescent alcohol consumption is predictive for alcohol problems later in life. To tailor interventions, early identification of risk groups for adolescent alcohol consumption is important. The IMAGEN dataset was utilized to investigate predictors for problematic alcohol consumption at age 18-20 years as a function self and parental personality and drug-related measures as well as life-events and cognitive variables all assessed at age 14 years (N=1,404).For this purpose the binary partitioning algorithm ctree was used in an explorative analysis. The algorithm recursively selects significant input variables and splits the outcome variable based on these, yielding a conditional inference tree. Four significant split variables, namely *Place of residence*, the *Disorganization* subscale of the Temperament and Character Inventory, *Sex*, and the *Sexuality* subscale of the life-events questionnaire were found to distinguish between adolescents scoring high or low on the Alcohol Use Disorders Identification Test about five years later (all $p < 0.001$). The analysis adds to the literature on predictors of adolescent drinking problems using a large European sample. The identified split variables could easily be collected in community samples. If their validity is proven in independent samples, they could facilitate intervention studies in the field of adolescent alcohol prevention.

Keywords: adolescence; alcohol consumption; conditional inference trees (ctree); hierarchical associations

1 Introduction

Elevated alcohol consumption during late adolescence is related to adult alcohol dependency and thus is associated with immediate and long-term negative consequences (for review, see McCambridge, McAlaney, & Rowe, 2011). Many interventions have been designed to prevent current and later alcohol misuse in adolescence (Foxcroft, Ireland, Lister-Sharp, Lowe, & Breen, 2003; Foxcroft & Tsertsvadze, 2012; Hawkins, Catalano, & Miller, 1992). Targeting these interventions more appropriately to adolescents at risk for high alcohol consumption could reduce costs and effort and thus make prevention programs more efficient. Moreover, identifying risk groups early during development may increase the time-window for interventions and therefore could facilitate more effective interventions.

Scientific knowledge about antecedent and risk factors for late adolescent alcohol consumption builds the basis to make interventions more effective. Previous work has revealed numerous risk factors in adolescence associated with initiation and level of alcohol consumption (e.g., Donovan, 2004; Newcomb, Maddahian, & Bentler, 1986). Although considered as lifetime-risk factors, higher levels of the personality traits impulsivity and sensation seeking are especially relevant in adolescence concerning binge drinking. This holds true independently of exact operationalization of this personality traits. With respect to the Big Five classification of personality, high extraversion has been most consistently related to binge drinking across studies, as well as high levels of neuroticism/low emotional stability. When considering variables especially predicting the *onset* of drinking (not changes in drinking behavior) Donovan (2004) described influential factors such as behavioral under-control, which can be operationalized as sensation seeking or impulsivity (for review, see Adan, Forero, & Navarro, 2017; Donovan, 2004). Apart from individual characteristics, psychosocial aspects have also been shown to be influential concerning (initiation of) drinking in adolescence. Among those are perceived approval of alcoholic beverages in the family, perceived parental drinking behavior, perceived greater parental permissiveness, and quality of child-parental relation (Donovan, 2004; Ryan, Jorm, & Lubman, 2010; Valente, Cogo-Moreira, & Sanchez, 2019). Besides family variables, peer variables have also proven influential in adolescent drinking behavior. Perceived peer attitudes towards drinking are important, as well as actual drinking behavior of peers

(Donovan, 2004). Cognition has come into focus as yet another influential aspect. Especially poor executive functioning has been related to alcohol use. (Poor) executive functioning as a cognitive measure of (poor) behavioral control has been shown to be related to (elevated) alcohol consumption in adolescence (e.g., Ellingson, Corley, Hewitt, & Friedman, 2019; Nigg, Wong, Martel, et al., 2006; Thush, Wiers, Ames, Grenard, Sussman, & Stacy, 2008). A recent paper by D'Agostino, Peterson, & Smith (2019) integrates the previously mentioned influential factors in a model in which negative urgency, that is, an individual's tendency to act rashly when distressed, and the expectation of drinking or smoking as calming, either learned by (parental/peer) modelling or by own experience and e.g. moderated by executive functioning, explains drinking behavior in adolescence. In this model, family variables, peer variables but also personality variables as well as cognitive aspects are integrated and considered influential. Another area of current research revealed evidence of large genetic influences on adolescent substance use disorders and their interplay with environmental influences. Research suggests that environmental influences are time-specific and variable whilst genetic influences remain relatively stable across time and largely contribute to the stability of alcohol use, however, still rather represent a predisposition than an inescapable fate (Hines, Morley, Mackie, & Lynskey, 2015; Zheng, Brendgen, Dionne, Boivin, & Vitaro, 2019). The interplay between genes and environment is nicely illustrated in a study by Davis and Slutske (2018), in which the genetic influence was reduced from about 50% of explained variance to about 2% of explained variance depending on low or high family income respectively.

Based on this work, the European research project IMAGEN specifically focused on adolescent development providing data especially suitable for the question of risk factors for late adolescent alcohol consumption. About 2000 adolescents were assessed from 14 years on with two follow-up measurements at age 16 and 18-20 (Schumann et al., 2010). Data collection included neuroimaging, genetic analyses, cognitive and behavioral tasks as well as questionnaires with a focus on drug and alcohol use. Different research groups have analyzed these data so far in order to determine predictors of adolescent alcohol consumption (Heinrich et al., 2016; Nees et al., 2012; Whelan et al., 2014). The first cross-sectional analysis by Nees and colleagues (2012) applied factor analysis and structural equation modeling in a group of 324

participants aged 14 years. Neural, behavioral and personality measures related to risk-taking and reward were included. These initial results suggested that each of the domains contributed to alcohol intake with personality explaining a higher proportion of the variance than behavior and brain responses. These findings were extended in the longitudinal analysis by Heinrich and colleagues (2016), using a sample of 736 participants. Structural equation modeling was used to predict alcohol consumption at age 14, age 16 and the increase between the two measurement occasions. Additional to the predictor variables examined by Nees and colleagues, candidate genes were added to the analysis. In line with the earlier findings personality was found to have the highest predictive value for alcohol drinking in early adolescence (age 14). With regard to alcohol consumption at age 16, personality and specific genetic variations were equally important predictors. Candidate genes had the highest predictive value for the increase in alcohol consumption between age 14 and age 16. A different methodological approach was taken by Whelan and colleagues (2015) to predict adolescent binge drinking. The authors applied machine learning in data from 692 participants assessed at age 14 and age 16. Brain structure and function, personality, cognition, environmental factors, life experiences, and candidate genes were included as predictors in the analyses. Life experiences, neurobiological variables and personality were identified as important predictors of current and later binge drinking with life experiences being the most predictive domain.

Not all predictor variables included in the above studies are suitable for large community samples because they need specialized equipment, such as a magnetic resonance imaging (MRI) scanner, or expensive blood analysis, such as genetics. Thus, the previous findings are very informative for the scientific community, but they cannot be easily applied in the field, testing the predictions in new samples of adolescents outside the laboratory. To overcome this drawback, we used a more applied perspective in the present analysis. First, we only included potential explanatory variables that can be easily assessed in large groups of individuals in the community (e.g., in schools). Second, we applied conditional inference trees to split the sample in a tree-based approach into groups differing in their later alcohol consumption. The algorithm determines not only the significant split variables, but also the optimal split criterion. Exact binary split criteria could facilitate the actual application of the present findings. Third, we

refrained from combining single variables (e.g., scores of personality questionnaires) to broader covariate domains (e.g., ‘Personality’) as commonly done in structural equation modelling, making it easier to utilize the present results for the selection of instruments in new samples, because only single questionnaires/tasks have to be assessed instead of a whole battery of variables representing each domain.

2 Materials and methods

2.1 Sample description

The analysis is based on the IMAGEN project, a longitudinal European multi-center study in adolescence (Schumann et al., 2010). About 2000 adolescents aged 14 years were included at eight sites in Europe (Dresden, Berlin, Mannheim, and Hamburg, Germany; London and Nottingham, U.K.; Dublin, Ireland; and Paris, France). Participants were tested with extensive neuropsychological assessments, completed personality questionnaires and underwent functional and structural neuroimaging. Blood samples for genetic and biological analyses were collected as well as psychological data from one parent of the participants (in above 80% by the mother, in about 17 % by the father and in below 2% by other adults, mostly step-mother, stepfather, or grandparents). Two follow-up assessments were conducted at age 15-16 (FU1) and age 18-20 (FU2). Written informed consent was obtained from all legal guardians and assent was obtained from the adolescents. Data from this project are stored on a data server operated according to European data protection law. Information about the procedures employed by the IMAGEN project (e.g., standardized instructions for administration of the psychometric and cognitive behavioral measures) is available in the standard operating procedures for the IMAGEN project (https://imagen-europe.com/standard-operating-procedures/).

2.2 Dataset

Participants with data available from the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) at FU2 (age 18-20) were included. Psychological and behavioral variables collected at baseline assessment (age 14) were included as potential explanatory variables in the analysis. Explanatory variables with more than 25% missing values were excluded.

2.2.1 Outcome variable/alcohol consumption:

The *AUDIT Total Score* derived from the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) at second follow-up (FU2) was chosen as the main outcome measure. The score comprises the sum of all items in the questionnaire and thus characterizes the individual

alcohol consumption, drinking behavior, and alcohol-related problems. *AUDIT Total Scores* were log-transformed prior to analysis due to a non-linear distribution.

2.2.2 Explanatory Variables:

The following variables were included as explanatory variables in the model (information on each variable is also described in Table 1). All variables except for age were measured at baseline assessment. The age of adolescents at baseline and follow-up measurement was included as two separate variables.

Demographics: *Age at baseline*, *Age at FU2*, *Sex*

Place of residence: Cities in which data were acquired were London, Nottingham, Dublin, Mannheim, Berlin, Hamburg, Paris and Dresden.

Socioeconomic status: The score contains the sum of the following variables: Mother's Education Score, Father's education score, Family financial crisis, Family Stresses: Unemployment, Family Stresses: Financial difficulties, Family Stresses: Home inadequate for needs, Family Stresses: Neighbours or neighbourhood (all provided by parents).

Tobacco use: Lifetime cigarette use was assessed with the question 'On how many occasions during your lifetime have you smoked cigarettes?' (6 answer options range from '0' to '40 or more').

Life events: The mean lifetime frequency of stressful events in the following domains was assessed using the life-events questionnaire (LEQ; adapted from Newcomb et al., 1981): *Family/Parents*, *Accident/Illness*, *Sexuality*, *Autonomy*, *Deviance*, *Relocation*, *Distress*, and *Events not subsumed under an event scale*.

Parental drug-related variables: Parental alcohol consumption was assessed with the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993). The following variables were included: *Frequency and hazardous Alcohol Use*, *Dependence Symptoms*, *Harmful Alcohol Use*.

Parents also completed the Michigan Alcoholism Screening Test (MAST; Selzer, 1971) from which the variable *Alcohol Dependency Symptoms* was included.

Parental cigarette use was assessed with the question 'On how many occasions during your lifetime have you smoked cigarettes?' (6 answer options range from '0' to '40 or more').

Personality measures: Variables from three personality questionnaires (all self-ratings) were included. Adolescent and parental personality scores were included as explanatory variables. The NEO five-factor inventory (NEO-FFI; Costa & McCrae, 1992) was used, which includes the variables *Neuroticism*, *Openness*, *Extraversion*, *Agreeableness*, and *Conscientiousness*. The Substance Use Risk Profile Scale (SURPS; Woicik et al., 2009) was used, including *Anxiety sensitivity*, *Impulsivity*, *Negative Thinking*, and *Sensation Seeking*. The four Novelty-seeking temperament subscales were used from the Temperament and Character Inventory – Revised (TCI-R; Cloninger, et al. 1999): *Impulsivity*, *Disorganization (Disorderliness)*, *Extravagance*, and *Exploratory Excitability*.

Cognition: Adolescents completed tasks of the Wechsler intelligence scale for children WISC-IV (Wechsler Intelligence Scale For Children–Fourth Edition (WISC-IV) The Psychological Corporation; 2003), from which the following subscales were included in the analysis: *Vocabulary*, *Similarities*, *Block Design*, *Matrix Reasoning*, and *Digit Span*.

Adolescents' performance in five tasks from the Cambridge Cognition Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition) was included as well: *Affective Go/No-go*, *Pattern Recognition Memory task*, *Spatial Working Memory Task*, *Rapid Visual Information Processing task*, and *Cambridge Gambling Task*.

Adolescents performed a *Stop Signal Task* assessing inhibitory control (adapted from Rubia et al. 2003, 2007) in the MR scanner. The task has been described in detail elsewhere (White et al., 2014).

A task named *IDENT* was performed by the adolescents (task was based on Pollak and Kistler (2002), containing new stimuli). In this task, a face morphed between two emotions appears on the screen and the subject has to decide which of the two emotions it looks most like. The emotions were anger, fear, happy, and sad, from which two were selected at a time. The mean

percent of trials in which the responses matched the identity of one emotion relative to the others was recorded.

Please insert Table 1 here

2.3. Analysis

Conditional Inference Tree (ctree, R package partykit: https://cran.r-project.org/web/packages/partykit/index.html; Hothorn & Zeileis 2015) was used to fit and visualize the association of alcohol consumption, as assessed by means of the *AUDIT Total Score* at age 18-20, and 66 explanatory (input) variables collected at age 14. Ctree is a recursive binary partitioning algorithm which we applied in an exploratory analysis. At first, the global null hypothesis of independence between all input variables and the outcome variable is tested. If it can be rejected, the algorithm selects the input variable with the strongest association to the outcome variable, in a way unbiased by the number of possible splits or missing values. Second, it implements a binary split in the selected input variable based on permutation tests. The algorithm recursively repeats these steps until the null-hypothesis of independence between the outcome and all input variables cannot be rejected at given α level (an α level of 0.001, Bonferroni-adjusted was used in this analysis). Detailed information on the method can be found elsewhere: https://cran.r-project.org/web/packages/partykit/vignettes/ctree.pdf.

A supplementary analysis used the AUDIT subscore measuring frequency and hazardous alcohol use (mean of AUDIT Item 1-3, *AUDIT frequency*) as outcome of a similar ctree analysis described above. We used this more objective measure of alcohol consumption to inspect whether the results of the main analysis might be specific to psychological aspects of drinking. *AUDIT Frequency* Scores were log-transformed prior to analysis due to a non-linear distribution.

3 Results

3.1 Sample description

Descriptive characteristics of the sample are provided in Table 2. The final sample consisted of 1404 adolescent participants (737 female, 667 male).

Supplementary Table S1 shows the percentage of missing data for all explanatory variables. One variable was excluded due to extraordinary high percent of missingness (>25%, *Fagerström questionnaire parents*).

Please insert Table 2 here

3.2 Ctree results

The resulting tree modeling *AUDIT* (log-transformed *AUDIT Total Score*) at age 18-20 as a function of the full set of explanatory variables is shown in Figure 1. Participants have been divided into six subgroups (terminal nodes 3, 4, 7, 8, 10, 11) according to the value of five split variables (inner nodes 1, 2, 5, 6, 9): *Place of residence* (node 1), *Disorganization (Disorderliness)* (TCI-R, node 2 and node 9), *Sex* (node 5), *Sexuality* domain of the LEQ (node 6). The first split (*Place of residence*) divides the data into two groups depending on the location the data have been acquired in ($p < 0.001$): Data acquisition center in the British Isles (London, Nottingham, Dublin) or data acquisition center in continental Europe (Berlin, Hamburg, Mannheim, Paris, Dresden). For participants from the British Isles the next division is made according to the level of *Disorganization* ($p < 0.001$). *Disorganization* levels above 25 go along with higher levels of alcohol consumption in this group. Participants from continental Europe were divided by *Sex* of participants ($p < 0.001$). Male participants have generally higher *AUDIT* scores than female participants and moreover subsequent splits differ between the sexes. Male participants from continental Europe are divided by the TCI-R variable *Disorganization*, with slightly differing split criteria compared to participants from the British Isles (≤ 21 / > 21 instead of ≤ 25 / > 25). For female participants from continental Europe a new split variable appears, namely the *Sexuality*

domain from the LEQ. Split criterion is ≤ 0 / > 0, with higher *AUDIT* scores for participants with *Sexuality* levels above zero.

Except for the split variable *Sexuality* from the LEQ, all splits were exactly (split variable and split criterion) replicated in the supplementary analysis using the log-transformed *AUDIT Frequency Score* as outcome. The results are shown in the Supplementary Figure S2.

The *AUDIT Total Scores* within the six final subgroups are described in Table 3. For easier interpretation, the AUDIT Scores have been transformed back to the original scale. The mean level of *AUDIT Total Scores* ranges from 3.20 (±2.35) to 9.10 (± 4.84) in these groups. The group with the lowest outcome scores is characterized by female participants from continental Europe with Sexuality scores in the LEQ ≤ 0. The highest outcome scores reach participants from the British Isles with Disorganization scores above 25. The table also depicts the percentage of each subgroup with *AUDIT Total Scores* equal or above eight, a recommended cut-off score for a variety of negative outcomes such as lifetime alcohol misuse (Conigrave, Hall, & Saunders, 1995). Proportion of individuals above this cut-off varies from 1.64 % in the group with the lowest outcome levels to almost 50 % (47.13 %) in the group with the highest levels.

To summarize, four variables from over 50 potential predictors are significantly associated with *AUDIT Total Scores* about five years later. The automatically implemented binary splits within these variables divide the sample into six subgroups that differ markedly in the outcome measure. The first split related to the countries in which participants lived during data collection makes clear that the findings are specific for the IMAGEN dataset and need to be replicated in independent samples.

Please insert Figure 1 here

Please insert Table 3 here

4 Discussion

We applied conditional inference trees to model alcohol use disorder symptoms as a function of self and parental personality and drug-related measures, life-events and cognitive variables collected during early adolescence. Based on binary splits, the sample of 1404 adolescents was divided into six groups differing in their mean Alcohol Use Disorder Identification (AUDIT) Score at age 18-20. The following variables were identified by the analysis as significant splits: *Place of residence*, *Disorganization (Disorderliness)* (TCI-R), *Sex*, *Sexuality* subscale (LEQ). The proportion of individuals with *AUDIT Scores* equal or above a cut-off of eight differs considerably between the subgroups defined by the splitting variables named above (from 1.6 % to 47.1 %). Generally, the findings replicate and expand the existing literature on predictors of adolescent alcohol problems and will be discussed in detail below. If they prove to be valid in future studies, they will help to identify adolescents at risk for high adolescent alcohol consumption early on.

The present analysis aimed at identifying risk factors for problematic drinking in older adolescents that can be easily collected in future field studies. Therefore, we investigated over fifty psychological variables including the domains personality, psychosocial variables, substance use, and cognition. Variable selection was based on previous findings of risk factors for adolescent alcohol consumption, taking into account individual characteristics such as personality, cognition, and psychosocial aspects such as parental drug use (e.g., Adan et al, 2017; Donovan, 2004, Thush et al., 2008). Variables that were significantly associated with the outcome measure were unbiasedly selected by the condition inference tree algorithm and a binary split was chosen by the method within these variables. The analysis focused on alcohol use disorder symptoms, but a supplementary analysis using a more objective measure of alcohol consumption within the same questionnaire revealed similar findings, highlighting that the observed risk factors are not attributable to psychological aspects of drinking alone.

First of all, the algorithm divided the sample into adolescents living on the British Isles (Great Britain, Ireland) and adolescents living in continental Europe namely Germany/France. The subsequent splits differed in some (though not all) instances in these two groups, indicating that place of living impacts the model parameters in the present sample. In general, mean alcohol

consumption at age 18-20 was higher in the two groups on the British Isles than in the four continental European groups. We would like to note that, despite their size, the IMAGEN subgroups in each country are not epidemiological samples. Thus, any differences between countries might be specific to this dataset and need to be replicated in further studies. Nevertheless, this finding is in line with previous reports noticing the impact of culture on individual drinking behavior (e.g., Ahlstrom & Osterberg, 2004; Kuntsche, Rehm, & Gmel, 2004) and differences in risk profiles between cultures (Vega, Zimmerman, Warheit, Apospori, & Gil 1993). Based on the present findings we suggest including environmental/cultural factors when investigating adolescent alcohol consumption. If precursors and predictors of late adolescent alcohol consumption differ between countries, country- and culture-specific models are needed to apply them effectively to the public, e.g., in intervention studies targeting high risk groups.

Across sites, *Disorganization*, a subscale from the Temperament and Character Inventory – Revised (TCI-R; Cloninger, et al. 1999) was revealed as a significant split variable. Within participants from continental Europe the variable was only significant for male adolescents. The four subscales of the TCI-R Novelty Seeking temperament (*Impulsivity*, *Disorganization* [*Disorderliness*], *Extravagance*, and *Exploratory Excitability*) had been included as potential predictors because previous findings indicate that Novelty Seeking is related to substance use and higher risk of adolescent alcohol consumption (Rose, 1998; Wills, Vaccaro, & McNamara, 1994). The TCI-R dimension Novelty Seeking was also revealed as a significant feature for adolescent alcohol consumption in two previous analyses using the IMAGEN sample (Nees et al., 2012; Whelan et al., 2014). Disorganization was also shown to be an especially good predictor for current and future binge drinking in the analysis by Whelan and colleagues (2014). The present analysis revealed concrete cut-off values for the subscale *Disorganization*, which were lower in the continental Europe male participants (cut-off 21) compared to the British Isle group (cut-off 25). In both groups, higher *Disorganization* levels at early adolescence (age 14) were associated with higher alcohol consumption at late adolescence (age 18-20). It remains an open question though, whether especially *Disorganization* as a subscale is the best predictor or if slightly different constructs generally describing “novelty seeking” and “impulsivity”, which have repeatedly been shown to be of importance, would be equally suited for the efficient,

community-sample-suited prediction in a ctree-model (see Adan et al., 2017; D'Agostino et al., 2019; Donovan, 2004 for different operationalization).

The last variable – the *Sexuality* domain of the life event questionnaire (LEQ, Newcomb et al., 1981) – splits the group of female participants from continental Europe. Example items for life events subsumed under this questionnaire domain are 'Fell in love', 'Got or made pregnant', and 'Broke up with boy/ girl-friend'. Only about 14 % of the correspondingly female participants did report that they had not experienced any of the events so far in their life. Those participants are characterized by lower alcohol consumption at age 18-20 compared to the group that did experience at least one of the Sexuality events. The result suggests a co-occurrence of no sexual experiences until age 14 and particular low alcohol consumption later, possibly accompanied by particular behavior and development in other drug-related and/or social domains. Because the group is very small and has a particular low level of alcohol consumption (the lowest in the total sample), we would not interpret the result the other way round implicating that having experienced at least one life event in the Sexuality domain increases the risk of high alcohol consumption later.

Sex differences in adolescent and adult alcohol consumption have been described and analyzed in previous investigations (Ceylan-Isik, McBride, & Ren, 2010; Inchley et al., 2016; Jackson, Sher, & Park, 2005). In the present analysis, *Sex* was a significant predictor variable only for participants from Germany/France. Male adolescents from these countries were generally characterized by higher alcohol consumption compared to female adolescents, which is in accordance with prior findings (e.g., Ceylan-Isik et al., 2010; Morean, Peterson, & L'Insalata, 2019; Wilsnack et al., 2009). It is interesting to notice that different further split variables occur for male and female adolescents. This finding supports research pointing to gender specific risk factors for alcohol consumption (e.g., Nolen-Hoeksema, 2004; Schulte, Ramo, & Brown, 2009). The results suggest a country-specific role of *Sex* in the prediction of alcohol consumption in the IMAGEN sample. This observation could explain why previous analyses of the data did not show overall sex differences in (or differences of the models predicting) adolescent alcohol consumption (Heinrich et al., 2016; Nees et al., 2012; Whelan et al., 2014). Future investigations

are needed that approach the question of why sex may play a role for future alcohol consumption in some groups of adolescents whereas it is not as important for other groups.

From the pool of over 50 psychological and cognitive variables, only four variables were identified as robust markers for later alcohol consumption. Lowering the statistical result threshold expectable leads to an increasing number of splits and split variables, but also causes more unstable results. Because the present analysis was exploratory, we decided to use a rather conservative p-value in combination with a large sample size to only identify the most robust and consistent split variables. With regard to the cognitive tasks included we would like to note that the results might look different if broader cognitive factors (e.g., verbal intelligence) would have been included instead of single task scores. To increase the applicability of our findings we were specifically interested in the predictive power of single tests, which are easier to administer.

The present results build on previous investigations on adolescent alcohol consumption that used the IMAGEN sample as well (Heinrich et al., 2016; Nees et al., 2012; Whelan et al., 2014). In contrast to the previous analyses, we included personality and psychological variables only, which enabled us to increase the sample size considerably (on minimum doubling the sample size compared to the previous analyses). The difference in variable selection of course limits the comparability of the present results with previous analyses. Moreover methodological differences between the analysis approaches hinder a direct comparison of results. The present analysis was based on ctree, a recursive partitioning algorithm implementing binary splits in the outcome variable. Besides methodological differences of this approach to structural equation modeling (used in previous analyses), results are also expected to overlap, if common variables are included that are significantly associated with alcohol consumption. Thus it is in line with the expectations that variable domains with high predictive power in previous analyses (e.g., personality measures) also showed up as significant split variables in the present investigation (e.g., TCI-R Disorganization). In addition, the present analysis has revealed new findings including the impact of *Site* on the model outcome. The present findings suggest that country-specific models should be used to investigate adolescent alcohol consumption in different European countries. The present analysis is a first step to determine variables able to distinguish

adolescents with low and high risk for high later alcohol consumption. A necessary further step is to test the split variables found in this study in an independent prospective study. To facilitate this approach, we only included variables that are relatively easily assessed in broad samples of adolescents (for instance in school classes). If the findings can be replicated, they provide basic knowledge for future research in the field of adolescent alcohol prevention. They can be used to target interventions to subgroups of adolescents at risk for later high alcohol consumption and thus make interventions more efficient. To give one example, the results suggest that males with high levels of *Disorganization* are at special risk to show high levels of alcohol use disorder symptoms later and therefore individuals with these characteristics could be a target group for a specific intervention.

Alcohol consumption at baseline assessment was not included as a potential predictor in the main analysis. The correlation of alcohol consumption across years within individuals in early and late adolescence has been demonstrated (e.g., Paavola, Vartiainen, & Haukkala, 2004; Pape, & Hammer, 1996). A specifically high correlation between this predictor and the outcome would have limited the potential of the analysis to reveal other variables predicting alcohol consumption. To test the impact of previous alcohol consumption in our sample, we included it as a predictor in a supplementary analysis (results are shown in Supplementary Figure S3). Alcohol consumption at baseline was assessed with the question 'On how many occasions in your whole lifetime have you had any alcoholic beverage to drink? '. The answer scale ranged from 0 (0 alcoholic drinks) to 6 (40 or more alcoholic drinks). The variable showed up as a significant split variable next to *Place of residence* and *Sex*. *Disorganization* (TCI-R) and the *Sexuality* domain of the LEQ were no longer significant. Previous alcohol consumption was relevant for all three subgroups defined by the other two split variables, with a slightly higher split criterion for females in continental Europe (split ≤3 / >3) compared to males from continental Europe (split ≤2 / >2) and individuals from the British Isles (split ≤2 / >2). The results of the supplementary analysis are in line with previous research and show that early adolescent alcohol consumption is as well a risk factor for problematic alcohol consumption in late adolescence.

We would like to outline some limitations of the present analysis. First, the analysis was exploratory and the results are based on prediction using a single dataset. Thus, confirmation of these findings in an independent dataset is crucial. Second, the high proportion of missing data for some of the predictor variables could have impacted the analysis, highlighting the importance to replicate the findings.

Third, we only investigated *one* outcome measure, the sumscore of the AUDIT self-report questionnaire. The results might look different for other aspects of adolescent alcohol consumption (e.g., binge drinking). To exemplarily test this notion, we reran the analysis with a single item from the AUDIT questionnaire assessing how often the participant has had six or more drinks on one occasion. The Item is related to the concept of binge drinking, which is commonly defined as "a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to 0.08 gram percent or above. For the typical adult, this pattern corresponds to consuming 5 or more drinks (male), or 4 or more drinks (female), in about 2 hours." (NIAAA, 2004, p 3). Using the Item as the outcome of the analysis leads to some changes in the resulting split variables. The Sexuality domain from the LEQ is no longer significant, the Disorganization score from the TCI-R is replaced by the Impulsivity score from the same questionnaire and the order of the variables Place of residence and Sex is interchanged (results of this analysis are shown in Supplementary Figure S2). This analysis illustrates that the predictive variables can vary depending on the aspect of problematic alcohol consumption chosen as the outcome.

To summarize, the present analysis modeled problematic adolescent alcohol consumption in a sample of 1404 adolescents (aged 18-20). A broad number of personality and drug-related measures, life-events and cognitive variables collected about four years before, were included as potential explanatory variables. The resulting conditional inference tree revealed three significant split variables dividing the adolescents according to their later alcohol consumption. The findings add to the literature on (early) predictors and risk factors of adolescent alcohol consumption and can be easily tested in new samples.

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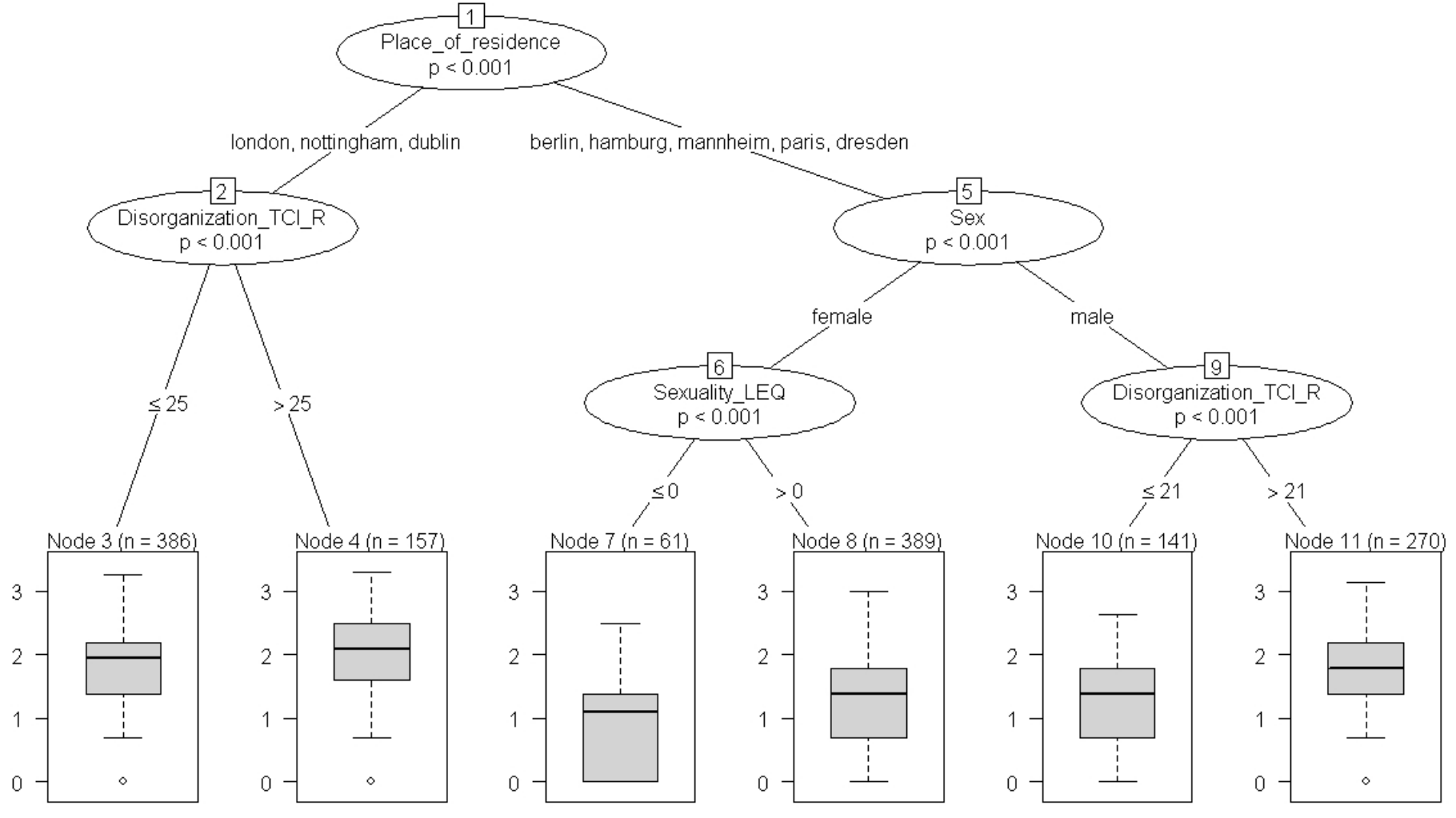

1
Place_of_residence
p < 0.001
london, nottingham, dublin
berlin, hamburg, mannheim, paris, dresden
2
Disorganization_TCI_R
p < 0.001
5
Sex
p < 0.001
≤ 25
> 25
female
male
6
Sexuality_LEQ
p < 0.001
9
Disorganization_TCI_R
p < 0.001
≤ 0
> 0
≤ 21
> 21
Node 3 (n = 386)
Node 4 (n = 157)
Node 7 (n = 61)
Node 8 (n = 389)
Node 10 (n = 141)
Node 11 (n = 270)
0
1
2
3

FIGURE CAPTION

Figure 1. Results of the ctree analysis predicting log-transformed *AUDIT Total Scores* at FU2 in the IMAGEN sample (age 18-20). Boxplots indicate median and interquartile range (IQR); whiskers cover values deviating less than 1.5 x IQR from the median.

Table I. Explanatory variables included as potential predictors in the model.

Variable	Task/ Questionnaire	Description of outcome measure
Age		Age in days
Sex		
Place of residence		Data acquisition center (London, Dublin, Nottingham, Paris, Berlin, Hamburg, Dresden, Mannheim)
SES		Socioeconomic status: Sumscore Mother's Education Score, Father's Education Score, Family Stress Unemployment Score, Financial Difficulties Score, Home Inadequacy Score, Neighborhood Score, Financial Crisis Score
Tobacco use		Number of lifetime occasions participant has smoked cigarettes
Life events		
Accident	LEQ	Mean lifetime frequency domain Accident
Autonomy	LEQ	Mean lifetime frequency domain Autonomy
Relocation	LEQ	Mean lifetime frequency domain Relocation
Family	LEQ	Mean lifetime frequency domain Family
Sexuality	LEQ	Mean lifetime frequency domain Sexuality
Deviance	LEQ	Mean lifetime frequency domain Deviance
Distress	LEQ	Mean lifetime frequency domain Distress
Noscale	LEQ	Mean lifetime frequency events not subsumed under an event scale
Drug-related (parents)		
Audit freq	AUDIT	Frequency and hazardous Alcohol Use
Audit prob	AUDIT	Harmful Alcohol Use
Audit symp	AUDIT	Dependence Symptoms
Ftnd sum	FTND	Nicotine dependency (Fagerström), sum
Tobacco use		Number of lifetime occasions parent has smoked cigarettes
Mast	MAST	Alcohol dependency symptoms (Michigan Alcoholism Screening Test), sum of all items
Personality measures		
Extraversion	NEO-PI-R	Mean, 5-point likert scale, 0-4
Agreeableness	NEO-PI-R	Mean

Neuroticism	NEO-PI-R	Mean
Openness	NEO-PI-R	Mean
Conscientiousness	NEO-PI-R	Mean
Anxiety seeking	SURPS	Mean, 4-point likert scale, 1-4
Impulsivity	SURPS	Mean
Negative thinking	SURPS	Mean
Sensation seeking	SURPS	Mean
Excitability	TCI-R	Sumscore, 5-point likert scale, 1-5
Extravagance	TCI-R	Sumscore
Impulsivity	TCI-R	Sumscore
Disorganization	TCI-R	Sumscore
Personality measures parents		
Extraversion	NEO-PI-R	Mean, 5-point likert scale, 0-4
Agreeableness	NEO-PI-R	Mean
Neuroticism	NEO-PI-R	Mean
Openness	NEO-PI-R	Mean
Conscientiousness	NEO-PI-R	Mean
Anxiety seeking	SURPS	Sumscore, 4-point likert scale, 1-4
Impulsivity	SURPS	Sumscore
Negative thinking	SURPS	Sumscore
Sensation seeking	SURPS	Sumscore
Excitability	TCI-R	Sumscore, 5-point likert scale, 1-5
Extravagance	TCI-R	Sumscore
Impulsivity	TCI-R	Sumscore
Disorganization	TCI-R	Sumscore
Cognition		
Vocabulary	WISC-IV	Raw score WISC-IV vocabulary test
Blockdesign	WISC-IV	Raw score WISC-IV blockdesign test
Matrixreasoning	WISC-IV	Raw score WISC-IV matrix reasoning test
Similarities	WISC-IV	Raw score WISC-IV similarieties test
Digitspan forward	WISC-IV	Raw score WISC-IV digitspan forward test
Digitspan longest forward	WISC-IV	Longest span WISC-IV digitspan forward test
Digitspan backward	WISC-IV	Raw score WISC-IV digitspan forward test

Digitspan longest backward	WISC-IV	Longest span WISC-IV digitspan backward test
AGN mean correct latency positive	CANTAB	Affective Go/No-go Task, The mean time (ms) taken to respond correctly to each target word stimulus in the positive blocks
AGN mean correct latency negative	CANTAB	Affective Go/No-go Task, The mean time (ms) taken to respond correctly to each target word stimulus in the negative blocks
PRM percent correct	CANTAB	Pattern recognition memory Task, percentage of correct responses
Foils recog	CANTAB	Pattern recognition memory Task , erroneous recognition of a previous pattern
SWM between errors	CANTAB	Spatial working memory Task, between-search errors (searching a box in which a token was found on a previous trial)
SWM strategy	CANTAB	Spatial working memory Task, Subjects' ability to adopt a consistent search strategy, (for problems with six boxes or more, the number of distinct boxes used by the subject to begin a new search for a token, within the same problem)
RVP sensitivity	CANTAB	Rapid Visual Information Processing Task, Prime (signal detection measure of sensitivity to the target, regardless of response tendency)
CGT risk taking	CANTAB	Cambridge Gambling Task, risk taking (percentage of the available points put at risk)
SST Success	Stop-Signal Task	Number of successful trials
SST Failure	Stop-Signal Task	Number of trials where subjects failed to stop and responded instead
SST Too early response	Stop-Signal Task	Stop trials where participants responded before the stop signal was shown
Anger fear threshold	IDENT Task	morph point anger-fear: mean percentage of trials in which responses matched the identity of the second emotion (fear) in the pair relative to the first emotion (anger) in the pair
Happy fear threshold	IDENT Task	s.a.
Anger sad threshold	IDENT Task	s.a.
Happy sad threshold	IDENT Task	s.a.

LEQ = Life-events questionnaire; AUDIT = Alcohol Use Disorders Identification Test; FTND = Fagerstrom Test for Nicotine Dependence; MAST = Michigan Alcoholism Screening Test; NEO-PI-R = revised NEO Personality Inventory; SURPS = Substance Use Risk Profile Scale; TCI-R = Temperament and Character Inventory – Revised; WISC-IV = Wechsler Intelligence Scale For Children–Fourth Edition; CANTAB = Cambridge Cognition Neuropsychological Test Automated Battery

Table II. Description of study sample.

Variable	Result
N	1404
Age (days) baseline	5265 (±163.3)
Age (days) FU2	6921(±267.8)
Sex	737 female, 667 male
Place of residence	London (182), Dublin (133), Nottingham (227), Paris (196), Berlin (128), Hamburg (182), Dresden (193), Mannheim (162)
Outcome: *Audit Total Score* FU2*	6.07 (±4.04), range 1-27

FU2=second follow-up assessment; * Data was log-transformed before analysis

Table III. Descriptive statistics of *Alcohol Total Scores* in the terminal nodes (subgroups).

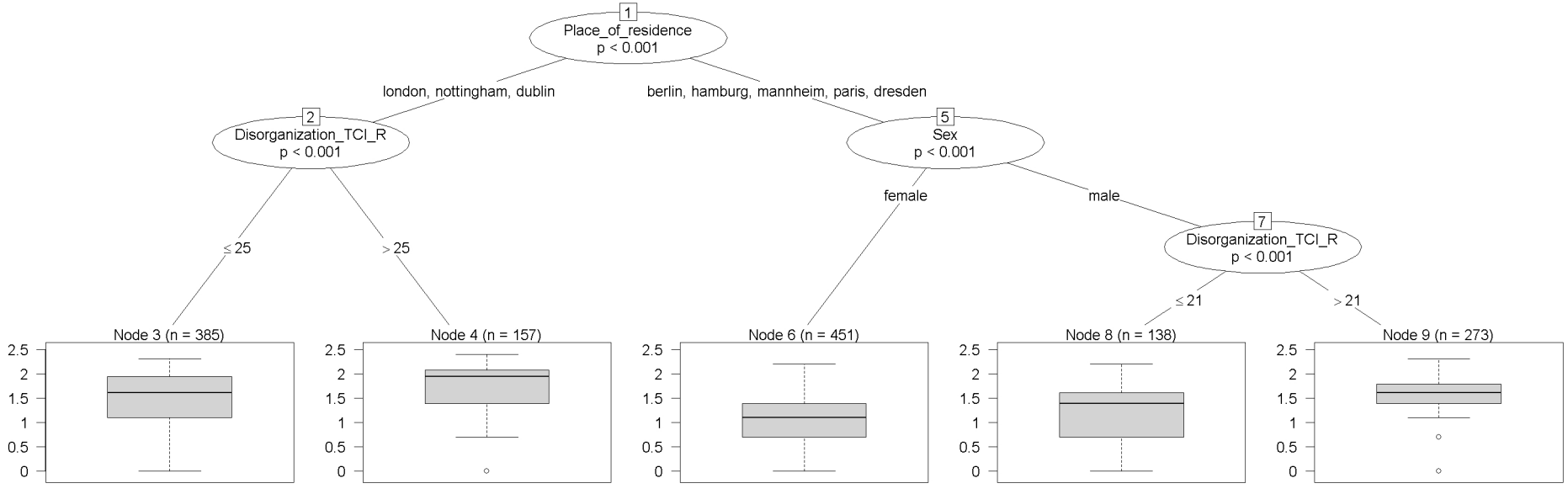
Node (N)	M (SD)	Range	% ≥ 8
3 (386)	7.06 (4.03)	1-26	31.37
4 (157)	9.10 (4.84)	1-27	47.13
7 (61)	3.20 (2.35)	1-12	1.64
8 (389)	4.45 (3.05)	1-20	9.51
10 (141)	4.74 (3.15)	1-14	12.06
11 (270)	6.56 (3.83)	1-23	25.93

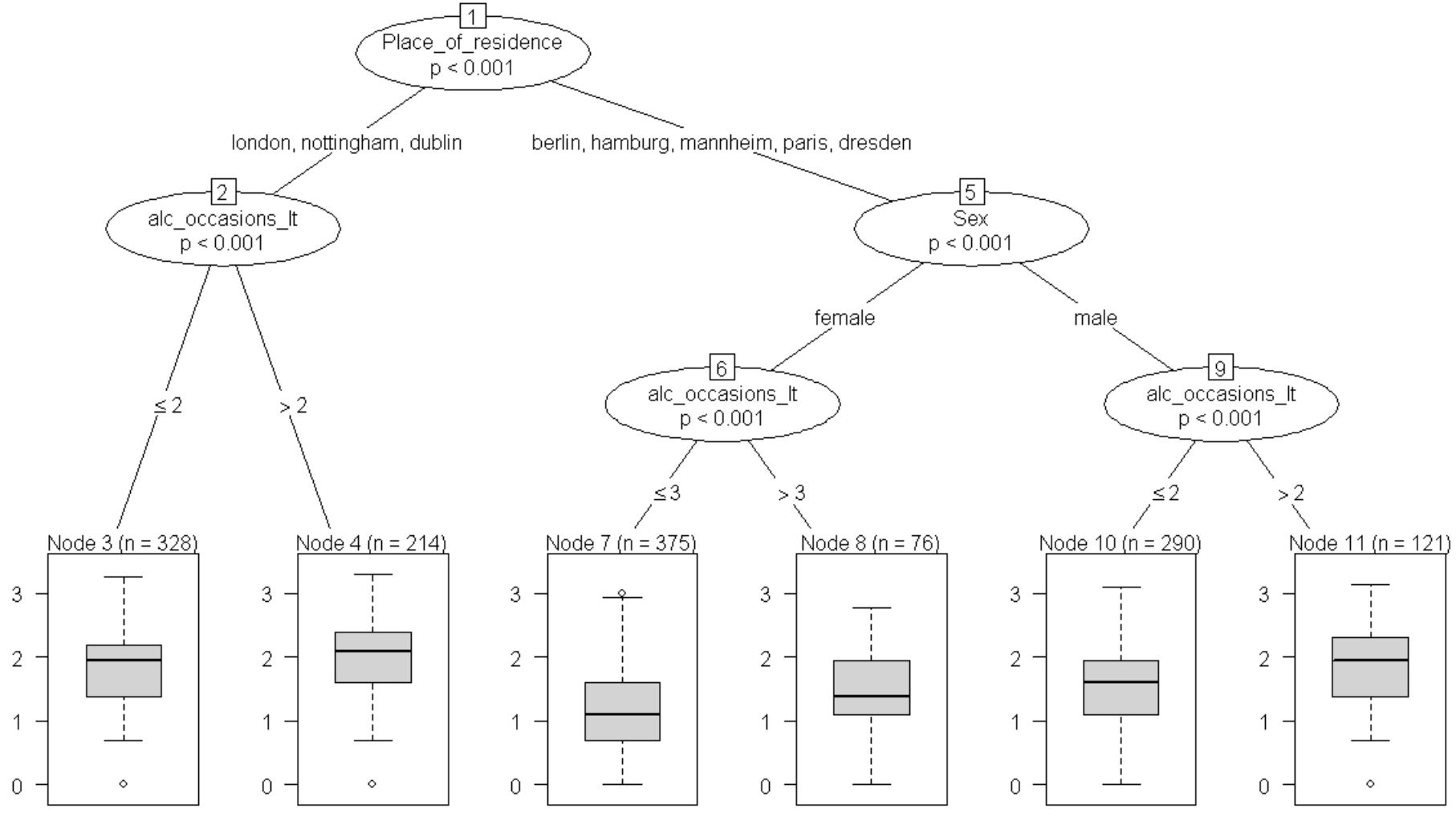
Conflict of interest

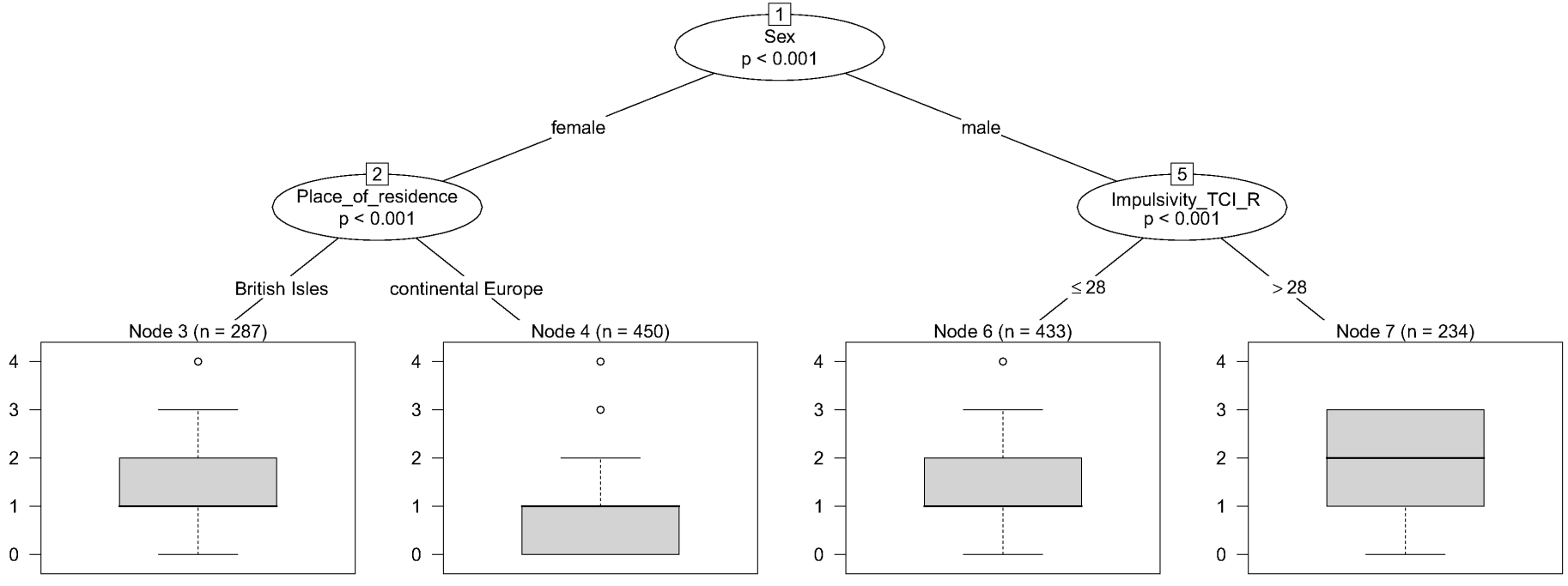
Dr. Banaschewski has served as an advisor or consultant to Bristol-Myers Squibb, Desitin Arzneimittel, Eli Lilly, Medice, Novartis, Pfizer, Shire, UCB, and Vifor Pharma; he has received conference attendance support, conference support, or speaking fees from Eli Lilly, Janssen McNeil, Medice, Novartis, Shire, and UCB; and he is involved in clinical trials conducted by Eli Lilly, Novartis, and Shire; the present work is unrelated to these relationships. Dr. Barker has received honoraria from General Electric for teaching on scanner programming courses. All other authors report no biomedical financial interests or potential conflicts of interest.

Author Agreement

All authors have read and approved the final version of the manuscript and agree to send in the submitted revision.


1
Place_of_residence
p < 0.001
london, nottingham, dublin
berlin, hamburg, mannheim, paris, dresden
2
Disorganization_TCI_R
p < 0.001
5
Sex
p < 0.001
≤ 25
> 25
female
male
7
Disorganization_TCI_R
p < 0.001
≤ 21
> 21
Node 3 (n = 385)
Node 4 (n = 157)
Node 6 (n = 451)
Node 8 (n = 138)
Node 9 (n = 273)
2.5
2
1.5
1
0.5
0


1
Place_of_residence
p < 0.001
london, nottingham, dublin
berlin, hamburg, mannheim, paris, dresden
2
alc_occasions_lt
p < 0.001
5
Sex
p < 0.001
≤ 2
> 2
female
male
6
alc_occasions_lt
p < 0.001
9
alc_occasions_lt
p < 0.001
≤ 3
> 3
≤ 2
> 2
Node 3 (n = 328)
Node 4 (n = 214)
Node 7 (n = 375)
Node 8 (n = 76)
Node 10 (n = 290)
Node 11 (n = 121)
0
1
2
3


1
Sex
p < 0.001
female
male
2
Place_of_residence
p < 0.001
5
Impulsivity_TCI_R
p < 0.001
British Isles
continental Europe
≤ 28
> 28
Node 3 (n = 287)
Node 4 (n = 450)
Node 6 (n = 433)
Node 7 (n = 234)
0
1
2
3
4

Supplementary Table S1. Missing values in percent for each predictor variable.

Variable	% missing data
Sex	0
Age baseline	4.91
Age FU2	5.20
Place of residence	0.07
SES	22.22
Tobacco use	0.43
LEQ: family	2.21
LEQ: accident	2.21
LEQ: sexuality	2.21
LEQ: autonomy	2.21
LEQ: deviance	2.21
LEQ: relocation	2.21
LEQ: distress	2.21
LEQ: noscale	2.21
NEO-PI-R: Extraversion	0.64
NEO-PI-R: Agreeableness	0.64
NEO-PI-R: Neuroticism	0.64
NEO-PI-R: Openness	0.64
NEO-PI-R: Conscientiousness	0.64
SURPS: Anxiety seeking	0.57
SURPS: Impuslivity	0.57
SURPS: Negative thinking	0.57
SURPS: Sensation seeking	0.57
TCI-R: Excitability	0.64
TCI-R: Extravagance	0.64
TCI-R: Impulsivity	0.64
TCI-R: Disorganization	0.64
TCI-R: Excitability	0.64
WISCIV: Similarities	3.28
WISCIV: Vocabulary	3.21
WISCIV: Blockdesign	3.21
WISCIV: Matrixreasoning	3.21
WISCIV: Digitspan forward	3.21
WISCIV: Digitspan backward	3.28
WISCIV: Digitspan longest forward	3.35
WISCIV: Digitspan longest backward	3.35
CANTAB: AGN mean correct latency positive	18.52
CANTAB: AGN mean correct latency negative	18.73
CANTAB: cgt risk taking	17.17
CANTAB: prm percent correct	5.91
CANTAB: rvp sensitivity	6.84
CANTAB: swm between errors	6.05
CANTAB: swm strategy	6.05
CANTAB: foils recog	7.05

SST: stop failure	4.42
SST: stop success	4.27
SST: stop too early response	13.96
IDENT: anger fear threshold	1.35
IDENT: anger sad threshold	1.35
IDENT: happy fear threshold	1.35
IDENT: happy sad threshold	1.35
Variables parents	
Mast	21.15
Tobacco use	1.00
Ftnd*	96.79
AUDIT: freq	7.98
AUDIT: prob	7.98
AUDIT: symp	7.98
NEO-PI-R: Extraversion	1.00
NEO-PI-R: Agreeableness	1.00
NEO-PI-R: Neuroticism	1.00
NEO-PI-R: Openness	1.00
NEO-PI-R: Conscientiousness	1.00
SURPS: Anxiety seeking	0.93
SURPS: Impuslivity	0.93
SURPS: Negative thinking	0.93
SURPS: Sensation seeking	0.93
TCI-R: Excitability	0.93
TCI-R: Extravagance	0.93
TCI-R: Impulsivity	0.93
TCI-R: Disorganization	0.93
TCI-R: Excitability	0.93

* Variable has been excluded because of too many missing values