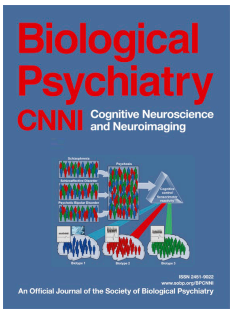
Journal Pre-proof



Chronic early-life obesity linked to childhood impulsivity predicts long-term psychosis trajectory through dose-dependent cerebellar dysmaturation in 22q11.2 Deletion Syndrome.

Corrado Sandini, M.D., Ph.D, Natacha Reich, MSc, Farnaz Delavari, M.D., Lara Pajic, M.D., Andrea Escelsior, M.D, Ph.D, Silas Forrer, MSc, Andrea Imparato, MSc, Nada Kojovic, PhD, Caren Latreche, MSc, Valeria Parlatini, M.D., Ph.D, Samuele Cortese, M.D., Ph.D, Maude Schneider, PhD, Stephan Eliez, M.D.

PII: S2451-9022(25)00262-9

DOI: https://doi.org/10.1016/j.bpsc.2025.08.014

Reference: BPSC 1481

To appear in: *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*

Received Date: 23 May 2025

Revised Date: 14 August 2025

Accepted Date: 19 August 2025

Please cite this article as: Sandini C., Reich N., Delavari F., Pajic L., Escelsior A., Forrer S., Imparato A., Kojovic N., Latreche C., Parlatini V., Cortese S., Schneider M. & Eliez S., Chronic early-life obesity linked to childhood impulsivity predicts long-term psychosis trajectory through dose-dependent cerebellar dysmaturation in 22q11.2 Deletion Syndrome., *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (2025), doi: https://doi.org/10.1016/j.bpsc.2025.08.014.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2025 Published by Elsevier Inc on behalf of Society of Biological Psychiatry.

Journal Pre-proof

Title: Chronic early-life obesity linked to childhood impulsivity predicts long-term psychosis trajectory through dose-dependent cerebellar dysmaturation in 22q11.2 Deletion Syndrome.

Running title: Childhood impulsivity, obesity and psychosis risk

Corrado Sandini M.D., Ph.D[1*] , Natacha Reich MSc[1*],Farnaz Delavari M.D.[1,2], Lara Pajic M.D.[1],, Andrea Escelsior M.D, Ph.D [3,4], Silas Forrer MSc[1,2], Andrea Imparato MSc[1], Nada Kojovic PhD[5], Caren Latreche MSc[1],Valeria Parlatini M.D., Ph.D [6,7,8,9], Samuele Cortese M.D., Ph.D [6,7,10,11,12], Maude Schneider PhD[13], Stephan Eliez M.D.[1,14]

[1] *Developmental Imaging and Psychopathology Laboratory, University of Geneva School of medicine, Geneva, Switzerland*

[2] *Medical Image Processing Laboratory, Institute of Bioengineering, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland*

[3]*IRCCS Ospedale Policlinico San Martino, Genoa, Italy*

[4]*Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, University of Genoa*

[5]*Autism Brain and Behavior (ABB) Lab, Department of Psychiatry, Faculty of Medicine, University of Geneva, Geneva, Switzerland*

[6]*Centre for Innovation in Mental Health, School of Psychology, University of Southampton, Southampton, SO17 1BJ, United Kingdom.*

[7] *Solent NHS Trust, Southampton, UK.*

[8] *Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, SE5 8AF, United Kingdom*

[9]*Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, SE5 8AF, United Kingdom.*

[10]*Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK.*

[11] *Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York, NY, USA.*

[12] *DiMePRe-J-Department of Precision and Regenerative Medicine-Jonic Area, University "Aldo Moro", Bari, Italy*

[13]*Clinical Psychology Unit for Intellectual and Developmental Disabilities, Faculty of Psychology and Educational Sciences, University of Geneva, Geneva, Switzerland*

[14] *Department of Genetic Medicine and Development, University of Geneva School of Medicine, Geneva, Switzerland*

Corresponding author: Corrado Sandini, Developmental Imaging and Psychopathology Laboratory, Department of Psychiatry, University of Geneva School of Medicine, Campus Biotech, Chemin des Mines 9, 1202 Geneva, Switzerland

*Shared First Author

Keywords: Schizophrenia; Cerebellum; BMI; Obesity; ADHD; Inflammation

Word Count: Abstract: 249, Main Text: 4443, 1 Table, 4 Figures

Journal Pre-proof

Abstract

Background: Recent epidemiological evidence links early-life obesity and metabolic dysregulation to adult psychosis vulnerability, though a causal relationship remains unclear. Establishing causality in highly heritable psychotic disorders requires: 1) demonstrating that early-life metabolic factors mediate between genetic vulnerability and psychosis trajectory, 2) dissecting mechanisms leading to early-life obesity in genetically vulnerable individuals, and 3) clarifying downstream neurodevelopmental pathways linking early-life obesity to psychosis symptoms.

Methods: Here we investigated bidirectional pathways linking behavioral, BMI, and neurodevelopment trajectories in a unique longitudinal cohort of 184 individuals at high genetic risk for psychosis, due to 22q11.2 Deletion Syndrome (22q11DS), and 182 neurotypical controls, followed-up since childhood. We combined repeated BMI measurements with clinical/neurocognitive phenotyping and neuroimaging. We investigated the relationship between BMI trajectories with risk of psychosis and tested whether altered cortical or cerebellar development could underlie this association.

Results: Childhood behavioral impulsivity predicted early and progressive deviations in BMI trajectories, mediating the effects of 22q11DS vulnerability to early-life obesity. Chronic BMI-increases manifesting during childhood predicted the subsequent emergence of psychosis during late-adolescence/early-adulthood, mediating the effects of behavioral impulsivity. A dose effect relationship linked duration of increased BMI-status to worsening of motor and cognitive disorganization, a key schizophrenia symptom domain, which was mediated by progressive gray matter volume reductions in posterior-inferior cerebellum.

Conclusions: These findings suggest that metabolic dysregulation associated with obesity may link childhood behavioral impulsivity to psychosis vulnerability in 22q11DS, by influencing cerebellar maturation. These findings might support preventive interventions targeting early-life metabolic trajectories in individuals at risk of psychosis.

Journal Pre-proof

Journal Pre-proof

Introduction

Obesity is consistently associated with various forms of psychopathology, including neurodevelopmental, mood, and psychotic disorders[1]. The causal directionality and mechanisms underlying these associations remain largely unclear. Indeed, metabolic dysregulation associated with obesity could contribute to the emergence of psychopathology, or be the result of altered caloric intake and expenditure in the context of psychiatric disorders[1, 2], or their treatment[3]. To clarify the direction of these associations, A key longitudinal study by Perry et al. followed over 14,000 individuals from birth to age 24, demonstrating that progressive increases in BMI during childhood were linked to elevated inflammatory markers and fasting insulin levels that persisted throughout adolescence[4]. These metabolic changes, in turn, led to a sixfold increase in the risk of developing psychosis in early adulthood [4]. These findings support a causal link between childhood obesity and later psychosis risk, likely mediated by prolonged immune-metabolic dysregulation, which if confirmed would have major clinical implications, as early-life metabolic trajectories can be effectively targeted through a variety of therapeutic and preventive public-health strategies[5]. Nevertheless, at least 3 key steps in this proposed causal pathway remain insufficiently clear[2] [4].

Firstly, although psychosis is highly heritable[6], it is not yet established whether early-life obesity serves as a mediator between genetic vulnerability and the clinical trajectory of psychosis [2]. The 22q11.2 Deletion Syndrome (22q11DS) offers a powerful model to investigate this question [7]. The genetic alterations associated with 22q11DS represent the single strongest genetic risk factor for psychosis, with an adult prevalence of psychotic disorders of 30-40%[8]. In parallel, 22q11DS is also linked to atypical early-life BMI trajectories leading to increased risk of adult obesity [9]. Currently, the association between behavioral and metabolic phenotypes of 22q11DS remains largely unclear. In this study, we investigated whether atypical BMI trajectories contribute to psychosis vulnerability in a well-characterized cohort of 184 individuals with 22q11DS and 182 healthy controls, assessed longitudinally from childhood to adulthood, comprising a total of 756 visits.

Second, the mechanisms leading to early-life obesity in genetically vulnerable individuals such as those with 22q11DS remain insufficiently understood [2]. Although the pathophysiology of pediatric obesity is complex and multifactorial [10], emerging clinical and genetic evidence[11, 12] increasingly implicate the role behavioral factors [13]. In particular, the hyperactivity/impulsivity dimensions of Attention-Deficit/Hyperactivity Disorder (ADHD), is a highly replicated risk factor for early-life obesity[14], which is directly corrected by ADHD treatment[14, 15], suggesting a disease specific causal mechanism[16]. It was proposed that behavioral impulsivity may foster obesity-predisposing eating patterns, contributing to deviant early-life BMI trajectories [17]. Notably, ADHD is present in about 30% of children with 22q11DS [8]. Here, we explored whether ADHD-related impulsivity predicts aberrant BMI trajectories in 22q11DS, and whether it mediates the impact of genetic risk for early-life obesity. Given accumulating evidence linking childhood ADHD to later psychosis risk in both the general population [18, 19] and in 22q11DS[20, 21], we further examined whether atypical BMI trajectories mediated the developmental link between childhood impulsivity and subsequent psychosis trajectory.

Finally, it remains unknown whether early-life obesity exerts a direct, dose-dependent effect on downstream neurodevelopmental pathways implicated in psychosis onset [2]. Of note, bot obesity and psychosis are associated with significant reductions of Gray-Matter-Volume (GMV) which, while not identical in their anatomical distribution, overlap in affecting Cerebellar-GMV[22, 23]. Recent data suggest that cerebellar GMV loss observed in first-episode psychosis may be driven, at least in part, by immune dysregulation associated with obesity [24], but the longitudinal studies required to dissect such 3-way interactions have not yet been conducted. In this study, we modeled cerebellar and cortical GMV trajectories from childhood to adulthood in individuals with 22q11DS, in relation to early-life BMI and psychiatric outcomes. We hypothesized that prolonged early-childhood obesity would exert a duration-dependent effect on gray-matter volume reductions, in particularly impacting the cerebellum, that would be specifically implicated in the emergence of disorganization symptoms of psychosis. Overall, we hypothesized the long-term multimodal phenotyping of individuals with 22q11DS would provide a unique view of developmental mechanisms linking ADHD-related behavioral impulsivity, to early-life obesity and subsequent psychosis vulnerability.

Journal Pre-proof

Methods

Participants:

In the present study, 372 participants, encompassing 184 participants with 22q11DS (M/F=93:91) and 188 Healthy Controls (HC) (M/F=92:96), were recruited as part of the Geneva-22q11DS-Longitudinal-Study[25] and followed-up prospectively for a total of 765 longitudinal assessments conducted in Geneva (433 in 22q11DS and 333 in HC). Table 1 reports participants' characteristics. Most (146/198) HC were recruited among unaffected siblings of 22q11DS participants.

Clinical and neurocognitive measures

Psychiatric diagnoses were assessed according to the DSM-5 (APA, 2013), with a combination of age-adapted semi-structured interviews detailed in the supplementary material. To further characterize clinical trajectories, we combined the Structured Interview for Prodromal Syndromes (SIPS)[26], the Brief Psychiatric Rating Scale (BPRS)[27], and the Child/Adult Behavior Checklist (CBCL/ABCL)[28]. Neurocognitive impulsivity was measured with the Conners' Continuous Performance Test 2nd edition (CPT2), considering age-normed T-Scores of Hit-Reaction-Time and of Commission/Omission errors [29]. Intelligent quotient (IQ) was measured using the Wechsler Intelligence Scale for Children (WISC-IV or V)[30] and Adults (WAIS-III or IV)[31].

Structural MRI Image Acquisition and Processing

T1-weighted images were acquired using Siemens Trio or Prisma 3T scanners (see Supplementary Material for details). Cerebellar segmentation followed the CERES method, implemented via the Volbrain MRI volumetry platform[32]. Gray Matter Volume (GMV) measures were extracted for the entire cerebellum and 12 lobules, averaged across hemispheres. Cortical segmentation was performed using Freesurfer (Version 7.4.1), with GMV extracted from 34 cortical regions [33] and averaged across hemispheres. High-quality cortical and cerebellar segmentation was available for 139 individuals with 22q11DS (254 assessments) and 135 Healthy Controls (187 assessments).

Statistical Analyses

Statistical analyses were conducted using MATLAB (version 2021a). To compare body mass index (BMI) trajectories between individuals with 22q11DS and healthy controls (HCs), we employed mixed-model linear regression (MMLR), implemented using a previously validated toolbox (https://github.com/danizoeller/myMixedModelsTrajectories). Statistical significance was established with likelihood ratio test with corresponding chi^2 statistics reported in the main text while standardized beta coefficient are reported in the supplementary material. In this model, BMI was expressed as a function of age, diagnosis, and their interaction, incorporating gender-specific diagnostic groups and a subject-specific random intercept: $BMI \sim Age*22q11DS_Male/Female + Age^2 * 22q11DS_Male/Female + Age^3 * 22q11DS_Male/Female + (1|Subject)$.We repeated this analysis in a subset of antipsychotic-naïve participants.

To investigate the clinical correlates of BMI, individuals with 22q11DS were categorized based on their BMI trajectories using a previously published classification pipeline[25]. We first generated average BMI trajectories for males and females. Each individual was then classified as having a high or low baseline BMI depending on whether their initial BMI was above or below their age- and sex-adjusted group trajectory. This approach was also applied to determine rate-of-change in BMI over time, considering only assessments during which participants were antipsychotic-naïve. This two-step classification yielded four trajectory-based subgroups: High- vs. Low-Baseline-BMI and Increasing- vs. Decreasing-BMI-Trajectory (Table-1).

We used MMLR to compare clinical symptom trajectories (19 SIPS items, 25 BPRS items, 10 CBCL/ABCL scales, 4 IQ indices, and 4 CPT scores) across BMI-defined 22q11DS subgroups, with the following structure:

Journal Pre-proof

*Clinical−Score~Age*BMI_Group_Male/Female+(1|Subject)*. False Discovery Rate (FDR) correction was applied within each psychometric scale[34]. A similar MMLR framework was employed to analyze cortical and cerebellar grey matter volume (GMV) trajectories, comparing both 22q11DS vs. HCs and 22q11DS BMI subgroups, accounting for scan type, sex, use of psychotropic medication, and intracranial volume.

To examine the lifetime emergence of major psychiatric disorders—including ADHD (inattentive and impulsive subtypes), depressive and anxiety disorders, and psychotic disorders—as well as major psychotropic medication classes (antipsychotics, psychostimulants, and SSRIs), we conducted Kaplan–Meier survival analyses, modelling diagnostic onset and medication initiation over age across 22q11DS BMI subgroups.

A series of second-level mediation analyses were conducted to examine how clinical and neurodevelopmental variables interact with BMI status in 22q11DS. All models were implemented in MATLAB using a linear mixed-effects framework with bootstrap inference (See Supplementary Materials for details).

The first model tested whether behavioral impulsivity mediated the association between 22q11DS diagnosis and BMI trajectory. Participants (22q11DS and HCs) were categorized into High or Low Externalizing-Problems groups based on lifetime CBCL/ABCL T-scores (>55). We compared BMI trajectories across these subgroups and tested whether the effects diagnostic group (22q11DS vs. HC), on BMI trajectory were mediated by high-vs-low Externalizing-Problems diagnosis. To explore potential causal influences, we further stratified the High-Externalizing 22q11DS group by lifetime exposure to psychostimulant treatment for ADHD.

The second model investigated whether BMI status mediated the effect of externalizing symptoms on subsequent clinical progression in 22q11DS. Externalizing subgroup over age served as the predictor, BMI group as the mediator, and symptom trajectories (SIPS or BPRS) as the outcomes.

A third model examined whether time spent in a high-BMI state more strongly predicted symptom progression and regional GMV changes than age alone, testing a potential dose–response effect. Here, baseline BMI group was the predictor, time since baseline was the mediator, and outcomes included SIPS/BPRS scores and regional GVM. These analyses were restricted to brain regions and clinical measures that showed significant BMI-by-age interactions in the first-level models.

Finally, we assessed whether cerebellar GMV changes mediated the relationship between BMI status and psychosis symptom trajectories. A multivariate Partial Least Squares (PLS) correlation analysis (https://github.com/valkebets/myPLS-1)[35, 36], identified cerebellar GMV patterns associated with SIPS symptom profiles, using 18 symptom items and GMV values from 12 cerebellar subfields. Imaging data were corrected for sex, scanner, medication use, intracranial volume, and subject-level random effects. Associations between multivariate Cerebellar-GMV and SIPS scores derived from the PLS analysis were modeled using MMLR: *Cerebellum_GMV_Score~SIPS_Symptom_Score+(1|Subject)*. We also examined whether this relationship was moderated by Baseline-BMI group status including quadratic terms to account for potential non-linear effects: *Cerebellum_GMV_Score~SIPS_Symptom_Score*Baseline_BMI+(SIPS_Symptom_Score)²*Baseline_BMI+(1|Subject)*. A final mediation model within the High-BMI subgroup tested whether cerebellar GMV mediated the relationship between age and progressive symptom intensification, with age as predictor, GMV score as mediator, and SIPS symptom severity as the outcome.

Results

Behavioral impulsivity predicts divergent BMI trajectories in 22q11DS

In both controls and individuals with 22q11DS, BMI followed a cubic trajectory, increasing during adolescence and stabilizing in adulthood (Figure-1-Panel-1A). However, individuals with 22q11DS exhibited steeper BMI increase from late childhood (Chi^2-Age-Interaction=27.66,p<0.001), resulting in higher BMI by early adulthood (Chi^2-Group-Effect =35.18,p<0.001). BMI increases preceded antipsychotic medication use and remained significant even in antipsychotic-naïve assessments (Figure-1-Panel-1B). Restricting BMI trajectory comparisons to a subsample of unrelated HCs yielded similar results (Supplementary-Figure-12).

BMI-Trajectory-Subgroups within the 22q11DS sample had similar baseline BMI but diverged in longitudinal trajectories (Chi^2-Age-Interaction=77.25,p<0.001), with the Female-Increasing-BMI-Subgroup showing the highest adult BMI (Chi^2-Group-Effect=86.96,p<0.001) (Figure-1-Panel-2B). Baseline-BMI-Subgroups differed in BMI scores from childhood (Chi^2-Group-Effect=100.04,p<0.001), with the Male-High-Baseline-BMI-Subgroup showing the most pronounced divergence over time (Chi^2-Age-Interaction=18.18,p<0.001) (Figure-1-Panel-2A).

Mean family income did not differ across BMI subgroups (Table-1). Family income and lifetime prevalence of hypothyroidism/diabetes did not differ, though hypoparathyroidism was elevated in High-Baseline-BMI individuals (Chi^2=5.1, *p*=0.02; Table-1).

ADHD with combined impulsivity (≥3 DSM-5 Impulsivity/Hyperactivity symptoms) was more frequent the High-Baseline-BMI (Chi^2-Group-Effect=5.37,p<0.02) and Increasing-BMI-Subgroups (Chi^2-Group-Effect=8.39,p=0.0038), particularly in Male-Increasing-BMI (55%) and Female-High-Baseline-BMI (47%) subgroups, while lowest in Female-Low-Baseline-BMI (10%) and Female-Decreasing-BMI (8.9%) subgroups (Figure-2-Panels-1A/2A). Purely inattentive ADHD rates were similar across BMI subgroups (Supplementary-Figures-3/4). DSM-5 Impulsivity/Hyperactivity symptoms were also significantly elevated in the High-Baseline-BMI (Chi^{2-}-Group-Effect=49.2,p<0.0001, Chi^2-Age-Interaction=6.07,p<0.0001) and Increasing-BMI-Subgroups (Chi^2-Group-Effect=9.6,p=0.022, Chi^2-Age-Interaction=8.4,p=0.015), whereas DSM-5 Inattention symptoms did not differ (Figure-2-Panels-1B/2B, Supplementary-Material).

Parental ratings in both High-Baseline and Increasing-BMI group revealed higher CBCL-Externalizing-Problems (Chi^2-Group-Baseline-BMI=6.19,p=0.012, Chi^2-Group-BMI-Trajectory=6.07,p=0.013) and CBCL-Aggressiveness (Chi^2-Group-Baseline-BMI=6.84,p=0.0078, Chi^2-Group-BMI-Trajectory=8.54,p=0.0034) scores (Figure-2-Panels-2C/D/3C/D and Supplementary-Figures-7).

Neurocognitive impulsivity in childhood was evident in High-Baseline-BMI and Increasing-BMI-Subgroups, with increased CPT-Commission/Omission-Errors (Chi^2-Group-Baseline-BMI=26.5,p<0.0001, Chi^2-Age-Interaction-Baseline-BMI=17.8,p<0.0001; Chi^2-Group-BMI-Trajectory=10.6,p=0.013, Chi^2-Age-Interaction-BMI-Trajectory=5.82,p=0.054), and lower Hit-Reaction-Time (Chi^2-Group-Baseline-BMI=18.8,p=0.0006, Chi^2-Age-Interaction-Baseline-BMI=12.1,p=0.0046; Chi^2-Group-BMI-Trajectory=11.1,p=0.011, Chi^2-Age-Interaction-BMI-Trajectory=8.25,p=0.01) (Figure-2-Panels-1E/1F and 2E/6F).

The High-Baseline-BMI subgroup also presented worsening attentional difficulties, reflected in progressively increasing CPT-Omission-Errors-T-Scores (Chi^2-Group-Baseline-BMI=30,p<0.0001, Chi^2-Age-Interaction-Baseline-BMI=18.3,p=0.0046) and Hit-Reaction-Time-T-Scores over time Chi^2-Group-Baseline-BMI=18.8,p<0.0001, Chi^2-Age-Interaction-Baseline-BMI=12.1,p<0.0001, along with a marginal reduction in Performance-IQ (Chi^2-Group-Baseline-BMI=3.92,p=0.047) driven by reduced Processing-Speed (Chi^2-Group-Baseline-BMI=6.27,p=0.012) (Supplementary-Figure-8).

We performed mediation analysis to explore the contribution of behavioral impulsivity to differences in BMI trajectories observed between 22q11DS and HCs. Clinically significant CBCL/ABCL Externalizing Problems, were significantly more prevalent in 22q11DS (115/65) than in Healthy-Controls (48/130) (Chi^2=49.2,p=2.32^{-12}) (Figure-2-Panel-3A). The High-Externalizing-22q11DS group had markedly increasing BMI compared to both 22q11DS-Low-Externalizing (Chi^2-Group-Effect=30.04,p<0.0001, Chi^2-Age-Interaction-Effect=20.26,p=0.0001) and to Healthy-Controls (Chi^2-Group-Effect=64.1 ,p<0.0001, Chi^2-Age-Interaction-Effect=47,p<0.0001), while 22q11DS-Low-Externalizing BMI trajectories were not significantly different from Healthy-Controls (Chi^2-Group-Effect=8.05,p=0.045, Chi^2-Age-Interaction-Effect=8.1,p=0.09) (Figure-2-Panel-3B).

Mediation analysis confirmed Externalizing Problems fully mediated the effect of 22q11DS diagnosis on BMI differences (indirect effect: β=0.05, 95%-CI=[0.009–0.11],p=0.012) (Figure-2-Panel-3C). Psychostimulant-treated individuals within the High-Externalizing group (n=37/100) had more typical BMI patterns, with delayed adiposity rebound compared to untreated peers (Chi^2-Group-Effect=10.35,p=0.035, Chi^2-Age-Interaction-Effect=9.99,p=0.019) (Figure-2-Panel-4). Results suggest that in 22q11DS genetic predisposition to early and progressive BMI increases, is mediated by genetic vulnerability to behavioral impulsivity, and can be partially rescued by psychostimulant ADHD treatment.

Chronic High-BMI status predicts psychosis vulnerability mediating genetic vulnerability.

The Increasing-BMI-Subgroup had significantly higher rates of Depressive Disorders (DD) (p=0.01), especially among adolescent females (30%), versus 13% in adult males with decreasing BMI (Chi^2=8.13,p=0.043) (Figure-3-Panel-1A). The Increasing-BMI-Subgroup exhibited age-related worsening of depressive symptoms, including SIPS-Dysphoric-Mood (Chi^2-Group=12.0,p=0.0016, Chi^2-Age-Interaction=4.27,p=0.038), BPRS-Depression (Chi^2-Group=16.3,p=0.0003, Chi^2-Age-Interaction=7.6,p=0.005), BPRS-Guilt (Chi^2-

Journal Pre-proof

Group=13.4,=0.0013, Chi^2-Age-Interaction=3.6,p=0.057), particularly in females (Figure-3-Panels-1B-D). Rates of Anxiety or Psychotic Disorders did not differ across BMI-Trajectory-Subgroups (Supplementary-Figure-4).

Although rates of Depressive or Anxiety diagnoses did not differ across Baseline-BMI subgroups, parentally reported CBCL-Internalizing-Problems were higher in the High-Baseline-BMI group (Supplementary-Figure-3/7). The High-Baseline-BMI-Subgroup had an increased 18% lifetime risk of psychotic disorder (PD) diagnosis, compared to 4% in the Low-Baseline-BMI-Subgroup (p=0.007, Chi^2=7.09, HR=3.79, CI=1.37-10.5). Within the High-Baseline-BMI-Subgroup, PD risk was highest in males (25%) versus females (10%) (Figure-3-Panel-2A). Despite being antipsychotic-naïve at baseline, the High-Baseline-BMI-Subgroup had a greater likelihood of receiving antipsychotic medication during follow-up up (P-Group-Effect=0.0005, P-Age-Interaction=0.0046), particularly in males (Chi^2 8.9, p-value 0.01) (Supplementary-Figure-2).

The High-Baseline-BMI-Subgroup also showed a progressive worsening of motor and thought disorganization symptoms, including BPRS-Motor-Retardation (Chi^2-Group=12,p=0.0025, Chi^2-Age-Interaction=11.5,p=0.0007), SIPS-Motor-Disturbances (Chi^2-Group=12.8,p=0.0016, Chi^2-Age-Interaction=8.9,p=0.0028) and SIPS-Bizarre-Thinking (Chi^2-Group=17.9,p<0.0001, Chi^2-Age-Interaction=12.5,p=0.0004) (Figure-3-Panels-2B-C-Left). Additional disorganization symptoms, including SIPS-Odd-Behavior (Chi^2-Group=11.9,p=0.0026, Chi^2-Age-Interaction=3,p=0.083), SIPS/BPRS-Self-Neglect, and SIPS-Disorganized-Communication, were elevated but showed no significant difference in age-related developmental trajectory (Supplementary-Table-1 and Supplementary-Figures-5/6). Interestingly, trajectories of several disorganization symptoms, including SIPS-Odd-Behavior (Chi^2-Group=19.5,p<0.0001, Chi^2-Time-from-Baseline-Interaction=9.9,p=0.0017) diverged significantly across Baseline-BMI-Subgroups, when modeled according to time from baseline assessment (Figure-3-Panels-2D-Middle. Supplementary-Figure-5). Indeed, formal mediation analysis confirmed that duration of High-BMI status mediated the effects of age, on progressive worsening of BPRS-Motor-Retardation, SIPS-Motor-Disturbances and SIPS-Bizarre-Thinking (Figure-3-Panels-2D-Right and Supplementary-Table-3). These results would suggest a dose-dependent relationship linking prolonged high-BMI to progressive worsening of disorganization symptoms ultimately associated with full-blown psychotic disorder diagnosis.

Finally, we investigated the interplay between childhood behavioral impulsivity High-Baseline-BMI status and psychosis vulnerability. The High-Externalizing-Problems subgroup presented increased vulnerability to lifetime full-blow psychotic disorders diagnosis (Ch^2=5.42,p=0.02), which was however significantly mediated the effects of High-Baseline-BMI status, (indirect effect: β=0.05, 95%-CI=[0.007–0.11],p=0.02). Indeed High-Baseline-BMI status mediated the effects of Externalizing-Problems on progressive worsening of SIPS-Bizarre-Thinking, SIPS-Motor-Disturbances and BPRS-Motor-Retardation, although Externalizing-Problems also contributed an additional effect on overall psychotic disorder vulnerability and SIPS-Bizarre-Thinking trajectory when accounting for High-BMI status (Figure-3-Panels-3 and Supplementary-Table-3).

Cerebellar maturation links prolonged High-BMI status to psychosis vulnerability

Compared to HCs, individuals with 22q11DS exhibited reduced cerebellar GMV, though age-related trajectories were not significantly different. Cortical GMV was also broadly reduced in 22q11DS, except in the orbitofrontal, insular, and precentral gyri, which showed increased volume. Age-related cortical GMV changes did not differ significantly after multiple comparisons correction (Supplementary-Tables-5-and-9 and Supplementary-Figure-9-and-11). BMI-Trajectory subgroups showed similar developmental trajectories for both cortical and cerebellar GMV, and no significant cortical differences emerged across Baseline-BMI groups. (Supplemementary-Tables-7-and-11 and Supplementary-Figure-9-10). However, the High-Baseline-BMI subgroup showed significant age-related reductions in posterior-inferior cerebellar regions, notably lobules VI and Crus I (Figure-3-Panel-4A), compared to both the Low-Baseline-BMI group (Crus-1-GMV: Chi^2-Group=10.9,p=0.01, Chi^2-Age-Interaction=10.2,p=0.01) and to HCs (Chi^2-Group=27.3,p<0.0001, Chi^2-Age-Interaction=12.5,p=0.0004). In contrast, the Low-Baseline-BMI group did not differ significantly from HCs in terms of age-related posterior-inferior GMV trajectories (Crus-1-GMV: Chi^2-Group=23.8,p<0.0001, Chi^2-Age-Interaction=1.3,p=0.51).

Journal Pre-proof

Differences in cerebellar GMV became more pronounced when analyzed as a function of time since baseline. Progressive reductions in total cerebellar GMV in the High-BMI group were driven by posterior-inferior lobules, particularly Crus I (Crus-1-GMV: Chi^2-Group=11.8,p=0.008, Chi^2-Age-Interaction=11.6,p=0.003) (Figure-3-Panel-4B). Mediation analysis confirmed that duration of high-BMI status mediated age-related GMV decline in lobules VI (indirect effect: β=-0.15, 95%-CI=[-0.29–0.013],p=0.034) and Crus-1 (indirect effect: β=-0.14, 95%-CI=[-0.27–0.07],p=0.04) (Figure-3-Panel-4C and Supplementary-Table-3).

To test whether cerebellar GMV mediated the link between high BMI and psychosis symptoms, we performed a partial least squares (PLS) analysis, which identified a significant latent component (R=0.26, p=0.049) linking reduced posterior-inferior GMV to increased severity in a symptom cluster including Odd-Behavior, Motor-Disturbances, Occupational-Functioning, Avolition, Blunted-Affect and Impaired-Tolerance-to-Stress (Figure-3-Panel-5B). A robust negative association was found between Cerebellum-GMV and SIPS-Symptom scores (β=-0.20 [-0.32/-0.08],p=0.001) (Figure-3-Panel-5C).

The lobules most affected by prolonged high BMI—VI, Crus I, I, and XI—were also key contributors to the PLS pattern (Figure-3-Panel-5A). The cerebellum–symptom association was stronger in the High-Baseline-BMI group (β=-0.26, 95%-CI=[-0.46/-0.04],p=0.01) compared to the Low-Baseline-BMI subgroup (β=-0.13 95%-CI=[-0.32/0.0008],p=0.051), with a significant group interaction effect (P-Group=0.046, P-Group-Cerebellum-GMV-interaction=0.026) (Figure-3-Panel-5C). Finally, in the High-Baseline-BMI group, cerebellar GMV reductions mediated the relationship between age and worsening SIPS symptom scores (indirect effect: β=0.16, 95%-CI=[0.002–0.55],p=0.044). (Figure-3-Panel-5D). These findings support a dose–response relationship, whereby prolonged high BMI leads to progressive cerebellar GMV loss, especially in posterior-inferior regions, which in turn increases vulnerability to psychosis through worsening of disorganization and negative symptoms.

Discussion

We explored the developmental impact of atypical BMI trajectories on psychosis vulnerability in a large longitudinal cohort of individuals with 22q11DS. The behavioral and neurocognitive impulsivity dimension of ADHD during childhood was associated with subsequent chronic BMI increases, mediating the effects of 22q11DS genetic vulnerability to early-life obesity. Childhood chronic High-BMI status contributed to a progressive increase in psychosis vulnerability, mediating the link between childhood impulsivity and subsequent psychosis clinical trajectory. A dose-effect relationship linked duration of prolonged High-BMI status to progressive alterations in cerebellar morphology, which were related to the development of motor and disorganization symptoms of psychosis. These results identify a novel neurodevelopmental-metabolic pathway linking childhood inhibitory control to psychosis vulnerability through cerebellar dysmaturation, described schematically in Figure 4.

Behavioral impulsivity predicts atypical BMI trajectories mediating the effects of 22q11DS genetic vulnerability

Recent studies in the general population suggest a significant overlap in the genetic underpinnings of ADHD with both obesity[11] and psychosis[18, 37] but the pathophysiological mechanisms accounting for these associations remain largely unclear. Our results show for the first time that in 22q11DS genetic vulnerability to early-life obesity is linked to the presence of behavioral and neurocognitive impulsivity during childhood. Indeed, both early BMI-increases and progressive increases in BMI scores were associated with diagnoses of impulsive ADHD, higher childhood externalizing psychopathology and neurocognitive trajectories indicative of childhood impulsivity. Moreover, childhood externalizing psychopathology mediated the effects of 22q11DS genetic vulnerability to atypical BMI trajectories. Atypical BMI trajectories associated with behavioral impulsivity were furthermore partially normalized by psychostimulant ADHD treatment, supporting an underlying causal association.

While these results are novel in 22q11DS, they are in line with evidence in the general population indicating that impulsivity/hyperactivity dimension of ADHD strongly predicts the emergence of early-life obesity[15], that can

be rescued by ADHD treatment[14]. It has been proposed that the impulsivity dimension of ADHD may contribute to impulsive eating patterns[17], which might reflect overleaping alterations in cortico-striatal circuits underlying top-down inhibitory control of feeding and goal directed behavior[38]. In accordance with these findings, our results suggest that the effects of 22q11DS early-life obesity genetic predisposition are mediated by behavioral impulsivity and can be at least partially rescued by behavioral impulsivity ADHD treatment.

Chronic High-BMI status predicts psychosis vulnerability mediating the effects of behavioral impulsivity.

Recent epidemiological evidence linked early deviations in metabolic trajectories to subsequent psychosis vulnerability[4]. However, behavioral phenotyping was only performed at the end of longitudinal follow-up, limiting the ability to characterize behavioral precursors of metabolic dysregulation[4]. The unique 22q11DS model allowed us to characterize both the metabolic and clinical trajectories preceding the emergence of psychosis. Early deviations in childhood BMI trajectories preceded and predicted the subsequent transition from prodromal symptoms to full-blown psychotic disorders occurring during adolescence/early-adulthood, which was more strongly related to the duration of high-BMI status than other age-related factors. These findings strongly argue against reverse causal mechanisms and would rather suggest a dose effect-relationship linking duration of High-BMI status to subsequent risk of psychosis[2, 4].

Of note, behavioral impulsivity mediated the effects of 22q11DS genetic vulnerability to atypical BMI trajectories, suggesting that chronic high-BMI status may serve as a key mediator between early-life behavioral impulsivity and later psychosis vulnerability. Indeed, converging epidemiological evidence suggests that ADHD and Psychosis share common genetic vulnerability[18], with childhood ADHD diagnosis increasing risk of psychotic disorders emerging during adolescence/early-adulthood[14, 19]. 22q11DS contributes to increased genetic risk for both ADHD and psychosis,[8] and evidence indicates that the impulsivity dimension of ADHD is predictive of subsequent disorganization symptoms associated with psychosis[20, 21]. Consistent with these findings, we observed a significant association between behavioral impulsivity and later psychosis vulnerability in individuals with 22q11DS. Crucially, this association was significantly mediated by the influence of behavioral impulsivity on early BMI trajectories, as well as by the downstream impact of prolonged high-BMI status on psychosis risk. This suggests that interventions aimed at reducing the influence of behavioral impulsivity on early-life BMI development could potentially mitigate the downstream psychiatric effects of overlapping ADHD and psychosis genetic vulnerabilities in 22q11DS.

Progressive Cerebellar atrophy links chronic High-BMI status to psychosis vulnerability.

We investigated neurodevelopmental mechanisms linking chronic High-BMI status to psychosis vulnerability. Individuals with prolonged High-BMI showed significant reductions in posterior-inferior Cerebellar-GMV compared to both low-BMI 22q11DS individuals and healthy controls. These effects were specific to Cerebellar-GMV and were not observed for Cerebral-Cortical-GMV. Moreover, cerebellar GMV reductions were more strongly associated with High-BMI duration than age, suggesting a dose-dependent effect of prolonged obesity on cerebellar atrophy. These findings align with prior evidence identifying posterior-inferior cerebellar atrophy as a shared neural correlate of both psychosis[23] and obesity[22]. Emerging evidence further suggests that cerebellar alterations observed in first-episode psychosis patients, may stem from co-occurring metabolic [24] and immunological dysregulation[39]. Additionally, cerebellar dysfunction could underly key hallmarks of psychosis symptomatology, including impaired adaptation of predictive models of the world based on past experience[40], leading to disorganized thought and behavior[41].

To explore this, we tested whether posterior-inferior cerebellar atrophy contributed to worsening of disorganization symptoms associated with prolonged high BMI status. Multivariate PLS analysis detected a significant association between Cerebellar-GMV atrophy and psychosis severity impacting a specific cluster of disorganization, negative, and motor symptoms. Of note, both symptoms and cerebellar subfields that contributed to this association were influenced by prolonged High-BMI status. Moreover, the relationship between cerebellar GMV atrophy and symptom severity was also significantly stronger in the high-Baseline-BMI subgroup. This suggests a disease process

linked to prolonged high-BMI status contributing to progressive cerebellar atrophy and associated worsening of disorganization, negative and motor symptoms. Indeed, a final mediation analysis confirmed that, within the High-Baseline-BMI subgroup, cerebellar GMV atrophy significantly mediated the effect of increasing age on progressive symptom worsening. These findings would suggest that cerebellar vulnerability to the adverse effects of prolonged high-BMI status underlies progressive worsening of disorganization, motor, and negative symptoms, culminating in psychosis onset.

At present, the underlying mechanisms through which high-BMI status impacts neurodevelopment remain speculative. Still, converging evidence implicate metabolic and immunological dysregulation. Elevated pro-inflammatory markers are observed at all stages of psychosis vulnerability[2], and may directly disrupt adolescent synaptic pruning implicated in psychosis pathophysiology[42], thereby predicting later psychosis onset in at-risk individuals[4, 43]. While the origins of immunological dysregulation in psychosis remain unclear[2, 44], obesity is widely recognized as a major risk factor for the development of chronic low-grade inflammation[45]. Given that childhood obesity often persists into adolescence and adulthood[46], obese children may be chronically exposed to pro-inflammatory states throughout critical periods of adolescent brain development[4]. Epidemiological data support this model indicating that adolescent insulin resistance and sustained inflammation mediated the link between high childhood BMI and adult psychosis vulnerability. [4]. While our study lacked direct metabolic and inflammatory measures to test this hypothesis explicitly, a triadic association among obesity, immunological dysregulation, and psychosis has recently been observed in individuals with 22q11DS[47].

Our findings suggest that the cerebellum may be particularly sensitive to the effects of metabolic and immunological dysregulation linked to prolonged obesity. This is consistent with translational evidence indicating heightened immunological vulnerability of the cerebellar cortex due to increased blood-brain-barrier permeability relative to the cerebral cortex[48]. Of note, 22q11DS is itself associated with altered blood-brain-barrier permeability [49], which may further exacerbate cerebellar susceptibility to the harmful immunological consequences of chronic obesity. This could, in turn, contribute to the progressive emergence of motor, cognitive, and behavioral disorganization symptoms—hallmarks of psychotic disorders—in individuals with prolonged High-BMI-status.

Strengths and Limitations

A major strength of this study is its long-term, multimodal, longitudinal design, which uniquely captures the developmental trajectory linking genetic vulnerability in 22q11DS to metabolic dysregulation, ADHD, and psychosis from childhood into adulthood. However, several limitations should be considered.

First, we lacked biochemical data on metabolic and immune dysregulation, which, according to our model, may mediate the impact of BMI on clinical and neurodevelopmental outcomes. While prior findings support a three-way association between BMI, immune dysregulation, and psychosis in 22q11DS[47], further research is needed to clarify these mechanisms.

Secondly, while our results suggest that behavioral impulsivity mediates the effect of 22q11DS on atypical BMI trajectories, we lacked detailed data on additional contributing factors—such as endocrinological, dietary, or lifestyle variables—that may influence BMI development[50] or moderate its association with behavioral impulsivity. For instance, preliminary results suggest higher prevalence of hypoparathyroidism in High vs Low Baseline-BMI subgroups, which warrants further investigation. Gender also appears to play a moderating role, consistent with epidemiological evidence indicating that associations between early metabolic dysregulation and psychosis risk may be stronger in males and post-pubertal BMI increases more strongly associated with depression in females [4]. It remains unclear whether these patterns reflect intrinsic gender differences in psychopathology, including increased female vulnerability to post-pubertal depression [51] and male vulnerability to childhood impulsivity[52] and early-onset psychosis[53], or differential moderating effects of gender on BMI–psychopathology associations.

Third, while our mediation analyses support a developmental pathway involving behavioral impulsivity, BMI, cerebellar changes, and psychosis risk, they also point to unmeasured contributing factors. Notably, a residual direct effect of impulsivity on psychosis vulnerability persisted after accounting for BMI, suggesting that additional

neurodevelopmental mechanisms may be involved and which should be investigated by combining additional neuroimaging modalities.

Fourth, while 22q11DS provides a rare model to study both antecedents and consequences of early BMI alterations, generalizability to the broader population is uncertain. Although our results align closely with epidemiological data linking early-life metabolic profiles to psychosis risk[4], specific features of 22q11DS—such as heightened immune sensitivity to obesity[45], or increased neuroinflammatory vulnerability due to blood–brain barrier alterations [49] may amplify the observed effects.

Despite these limitations, our findings emphasize the need to further investigate the role of metabolic dysregulation in the developmental trajectory of ADHD and its association with psychosis risk, both within and beyond 22q11DS. Clinically, the results raise the possibility that addressing metabolic consequences of impulsivity in early life could reduce psychosis vulnerability. While this remains a hypothesis, our findings provide a compelling rationale for preventive trials targeting early-life obesity to mitigate long-term psychiatric risk.

Acknowledgments:

This study was supported by the Swiss National Science Foundation (SNSF) (Grant numbers: to SE FNS 320030_179404, FNS 324730_144260) and by the National Center of Competence in Research (NCCR) Synapsy-The Synaptic Bases of Mental Diseases (Grant number: 51AU40_125759). Prof Maude Schneider (#162006) and Dr Corrado Sandini (#209096) were supported by grants from the SNF. Samuele Cortese, NIHR Research Professor (NIHR303122) is funded by the NIHR for this research project. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, NHS or the UK Department of Health and Social Care. Samuele Cortese is also supported by NIHR grants NIHR203684, NIHR203035, NIHR130077, NIHR128472, RP-PG-0618-20003 and by grant 101095568-HORIZONHLTH- 2022-DISEASE-07-03 from the European Research Executive Agency. Figure-4 is created with Biorender.com. We warmly thank all the families who participated in the study.

Conflict of interest

Prof. Cortese has declared reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) in relation to lectures delivered for ACAMH, the Canadian AADHD Alliance Resource, the British Association of Psychopharmacology, and from Healthcare Convention for educational activity on ADHD, and has received honoraria from Medice. All other authors report no biomedical financial interests or potential conflicts of interest.

Supplement Description:

Supplement Methods, Results, Figures S1-S12, Tables S1-S12

Journal Pre-proof

Journal Pre-proof

References

1. Leutner, M., et al., *Obesity as pleiotropic risk state for metabolic and mental health throughout life.* Transl Psychiatry, 2023. **13**(1): p. 175.
2. Pillinger, T., et al., *Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models.* Mol Psychiatry, 2019. **24**(6): p. 776-794.
3. Pillinger, T., et al., *Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis.* The Lancet Psychiatry, 2020. **7**(1): p. 64-77.
4. Perry, B.I., et al., *Longitudinal Trends in Childhood Insulin Levels and Body Mass Index and Associations With Risks of Psychosis and Depression in Young Adults.* JAMA Psychiatry, 2021. **78**(4): p. 416-425.
5. Lambrinou, C.P., et al., *Effective strategies for childhood obesity prevention via school based, family involved interventions: a critical review for the development of the Feel4Diabetes-study school based component.* BMC Endocr Disord, 2020. **20**(Suppl 2): p. 52.
6. Gottesman, II and J. Shields, *A polygenic theory of schizophrenia.* Proc Natl Acad Sci U S A, 1967. **58**(1): p. 199-205.
7. McDonald-McGinn, D.M., et al., *22q11.2 deletion syndrome.* Nat Rev Dis Primers, 2015. **1**: p. 15071.
8. Schneider, M., et al., *Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome.* Am J Psychiatry, 2014. **171**(6): p. 627-39.
9. Tarquinio, D.C., et al., *Growth charts for 22q11 deletion syndrome.* Am J Med Genet A, 2012. **158A**(11): p. 2672-81.
10. Gonzalez-Muniesa, P., et al., *Obesity.* Nat Rev Dis Primers, 2017. **3**: p. 17034.
11. Anttila, V., et al., *Analysis of shared heritability in common disorders of the brain.* Science, 2018. **360**(6395).
12. Karlsson Linner, R., et al., *Multivariate analysis of 1.5 million people identifies genetic associations with traits related to self-regulation and addiction.* Nat Neurosci, 2021. **24**(10): p. 1367-1376.
13. Berthoud, H.R., H. Munzberg, and C.D. Morrison, *Blaming the Brain for Obesity: Integration of Hedonic and Homeostatic Mechanisms.* Gastroenterology, 2017. **152**(7): p. 1728-1738.
14. Cortese, S., et al., *Association Between ADHD and Obesity: A Systematic Review and Meta-Analysis.* Am J Psychiatry, 2016. **173**(1): p. 34-43.
15. Kase, B.E., et al., *Longitudinal Associations Between Symptoms of ADHD and BMI From Late Childhood to Early Adulthood.* Pediatrics, 2021. **147**(6).
16. Cortese, S. and B. Vincenzi, *Obesity and ADHD: clinical and neurobiological implications.* Curr Top Behav Neurosci, 2012. **9**: p. 199-218.
17. Pinto, S., et al., *Eating Patterns and Dietary Interventions in ADHD: A Narrative Review.* Nutrients, 2022. **14**(20).

Journal Pre-proof

18. Olde Loohuis, L.M., et al., *Genetic and clinical analyses of psychosis spectrum symptoms in a large multiethnic youth cohort reveal significant link with ADHD.* Transl Psychiatry, 2021. **11**(1): p. 80.
19. Nourredine, M., et al., *Association of Attention-Deficit/Hyperactivity Disorder in Childhood and Adolescence With the Risk of Subsequent Psychotic Disorder: A Systematic Review and Meta-analysis.* JAMA Psychiatry, 2021. **78**(5): p. 519-529.
20. Niarchou, M., et al., *Attention deficit hyperactivity disorder symptoms as antecedents of later psychotic outcomes in 22q11.2 deletion syndrome.* Schizophr Res, 2019. **204**: p. 320-325.
21. Niarchou, M., et al., *Attention Deficit Hyperactivity Disorder Symptoms and Psychosis in 22q11.2 Deletion Syndrome.* Schizophr Bull, 2018. **44**(4): p. 824-833.
22. Garcia-Garcia, I., et al., *Neuroanatomical differences in obesity: meta-analytic findings and their validation in an independent dataset.* Int J Obes (Lond), 2019. **43**(5): p. 943-951.
23. Moberget, T., et al., *Cerebellar volume and cerebellocerebral structural covariance in schizophrenia: a multisite mega-analysis of 983 patients and 1349 healthy controls.* Mol Psychiatry, 2018. **23**(6): p. 1512-1520.
24. Kolenic, M., et al., *Higher Body-Mass Index and Lower Gray Matter Volumes in First Episode of Psychosis.* Front Psychiatry, 2020. **11**: p. 556759.
25. Sandini, C., et al., *Pituitary dysmaturation affects psychopathology and neurodevelopment in 22q11.2 Deletion Syndrome.* Psychoneuroendocrinology, 2020. **113**: p. 104540.
26. Miller, T.J., et al., *Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity.* Am J Psychiatry, 2002. **159**(5): p. 863-5.
27. Overall, J.E. and D.R. Gorham, *The Brief Psychiatric Rating Scale.* Psychological Reports, 1962. **10**(3): p. 799-812.
28. TM, A., *Manual for the Child Behavior Checklist/4-18 and 1991 profile*. 1991: Burlington: University of Vermont Department of Psychiatry.
29. Keith Conners, C., G. Sitarenios, and L.E. Ayearst, *Conners' Continuous Performance Test Third Edition*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2018, Springer International Publishing: Cham. p. 929-933.
30. D, W., *The Wechsler intelligence scale for children—third edition: administration and scoring manual.* 1991, San Antonio: Psychological corporation.
31. D., W., *Wechsler adult intelligence scale-III: administration and scoring manual.* 1997, San Antonio: Psychological Corporation.
32. Manjón, J.V. and P. Coupé, *volBrain: An Online MRI Brain Volumetry System.* Front Neuroinform, 2016. **10**: p. 30.
33. Desikan, R.S., 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): p. 968-80.
34. Benjamini, Y. and D. and Yekutieli, *False Discovery Rate–Adjusted Multiple Confidence Intervals for Selected Parameters.* Journal of the American Statistical Association, 2005. **100**(469): p. 71-81.

Journal Pre-proof

35. Delavari, F., et al., *Dysmaturation Observed as Altered Hippocampal Functional Connectivity at Rest Is Associated With the Emergence of Positive Psychotic Symptoms in Patients With 22q11 Deletion Syndrome.* Biol Psychiatry, 2021. **90**(1): p. 58-68.
36. Zoller, D., et al., *Psychotic symptoms influence the development of anterior cingulate BOLD variability in 22q11.2 deletion syndrome.* Schizophr Res, 2017.
37. Hamshere, M.L., et al., *Shared polygenic contribution between childhood attention-deficit hyperactivity disorder and adult schizophrenia.* Br J Psychiatry, 2013. **203**(2): p. 107-11.
38. Barbosa, D.A.N., et al., *Aberrant impulse control circuitry in obesity.* Mol Psychiatry, 2022. **27**(8): p. 3374-3384.
39. Quide, Y., et al., *Systemic inflammation and grey matter volume in schizophrenia and bipolar disorder: Moderation by childhood trauma severity.* Prog Neuropsychopharmacol Biol Psychiatry, 2021. **105**: p. 110013.
40. Schmahmann, J.D., *Dysmetria of thought: clinical consequences of cerebellar dysfunction on cognition and affect.* Trends Cogn Sci, 1998. **2**(9): p. 362-71.
41. Andreasen, N.C., et al., *Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms.* Biol Psychiatry, 1999. **46**(7): p. 908-20.
42. Sekar, A., et al., *Schizophrenia risk from complex variation of complement component 4.* Nature, 2016. **530**(7589): p. 177-83.
43. Kappelmann, N., et al., *Systemic inflammation and intelligence in early adulthood and subsequent risk of schizophrenia and other non-affective psychoses: a longitudinal cohort and co-relative study.* Psychol Med, 2019. **49**(2): p. 295-302.
44. Khandaker, G.M., et al., *Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment.* Lancet Psychiatry, 2015. **2**(3): p. 258-270.
45. Hotamisligil, G.S., *Inflammation and metabolic disorders.* Nature, 2006. **444**(7121): p. 860-7.
46. Rolland-Cachera, M.F., et al., *Early adiposity rebound: causes and consequences for obesity in children and adults.* Int J Obes (Lond), 2006. **30 Suppl 4**: p. S11-7.
47. Mekori-Domachevsky, E., et al., *Elevated Proinflammatory Markers in 22q11.2 Deletion Syndrome Are Associated With Psychosis and Cognitive Deficits.* J Clin Psychiatry, 2017. **78**(9): p. e1219-e1225.
48. Phares, T.W., et al., *Regional differences in blood-brain barrier permeability changes and inflammation in the apathogenic clearance of virus from the central nervous system.* J Immunol, 2006. **176**(12): p. 7666-75.
49. Crockett, A.M., et al., *Disruption of the blood-brain barrier in 22q11.2 deletion syndrome.* Brain, 2021. **144**(5): p. 1351-1360.
50. Kim, M.S., et al., *Association of genetic risk, lifestyle, and their interaction with obesity and obesity-related morbidities.* Cell Metab, 2024. **36**(7): p. 1494-1503 e3.
51. Salk, R.H., J.S. Hyde, and L.Y. Abramson, *Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms.* Psychol Bull, 2017. **143**(8): p. 783-822.
52. Cross, C.P., L.T. Copping, and A. Campbell, *Sex differences in impulsivity: a meta-analysis.* Psychol Bull, 2011. **137**(1): p. 97-130.
53. Selvendra, A., et al., *Age of onset by sex in schizophrenia: Proximal and distal characteristics.* J Psychiatr Res, 2022. **151**: p. 454-460.

Journal Pre-proof

Journal Pre-proof

Table Legends:

Table 1: Demographic information. Differences in continuous measures were tested using a two-samples t-test, while binary measures were tested using a Chi^2 test. Household incomes are scaled from 1 to 10 (with 1<15'000 CHF/year and 10 > 240'000 CHF/year). Education is scaled from 1 to 7 (1 = primary school, 2=middle school, 3-4=High School, 5-6 = University and 7 = PhD).

1 Two-samples t-test

^{2} Chi^2 test

* Significant difference ($p<0.05$)

Figure Legends:

Figure 1:

Panel 1A: Developmental trajectories of BMI scores compared across Healthy Controls and 22q11DS individuals modelling for the effects of gender yielding 4 subgroups: Male 22q11DS in dark blue, Female 22q11DS in red, Male Healthy Controls in Light Blue, Female Healthy Controls in Orange. Assessments during which 22q11DS individuals are receiving antipsychotic treatment are highlighted in black.

Panel 1B: Developmental trajectories of BMI scores compared across Healthy Controls and 22q11DS individuals still naïve to antipsychotic medication.

Panel 2A: Subgroup analysis within 22q11DS sample. 22q11DS are divided in subgroups according to BMI scores at baseline assessments and considering males and females separately. This analysis yields 4 subgroups, High-Baseline BMI-Males in dark blue, High-Baseline-BMI-Females in red, Low-Baseline-BMI-Males in light blue, and Low-Baseline-BMI-Females in orange.

Panel 2B: Subgroup analysis within 22q11DS sample. 22q11DS are divided in subgroups according to longitudinal BMI trajectories, considering males and females separately. This analysis yields 4 subgroups, Increasing-BMI-Males in dark blue, Increasing-BMI-Females in red, Decreasing-BMI-Males in light blue, and Decreasing-BMI-Females in orange.

Figure 2:

Evidence that atypical BMI trajectories are linked to childhood behavioral and neurocognitive impulsivity.

Panels 1A-1F: Behavioral and neurocognitive impulsivity in High-vs-Low-Baseline-BMI subgroups. High-Baseline BMI-Males in dark blue, High-Baseline-BMI-Females in red, Low-Baseline-BMI-Males in light blue, and Low-Baseline-BMI-Females in orange.

Journal Pre-proof

Panels 2A-2F: Behavioral and neurocognitive impulsivity in Increasing-vs-Decreasing-BMI-Trajectory subgroups. Increasing-BMI-Males in dark blue, Increasing-BMI-Females in red, Decreasing-BMI-Males in light blue, and Decreasing-BMI-Females in orange.

Panels 1A-2A: Kaplan-Meyer survival curves for lifetime DSM-5 diagnosis of ADHD associated with 3 or more impulsivity/hyperactivity symptoms.

Panels 1B-2B: Number of DSM-5 impulsivity/hyperactivity symptoms compared across BMI-Subgroups with Mixed-Model-Linear-Regression.

Panels 1C-2C: Parentally reported Aggressiveness considering age-normed Child-Behavioral-Checklist T-Score compared across BMI-Subgroups with Mixed-Model-Linear-Regression.

Panels 1D-2D: Parentally reported Externalizing Problems considering age-normed Child-Behavioral-Checklist T-Score compared across BMI-Subgroups with Mixed-Model-Linear-Regression.

Panels 1E-2E: Ratio of CPT2 Commission/Omission Error T-Scores measuring neurocognitive impulsivity compared across BMI-Subgroups with Mixed-Model-Linear-Regression.

Panels 1F-2F: CPT2 Hit-Reaction-Time T-Scores measuring neurocognitive impulsivity compared across BMI-Subgroups with Mixed-Model-Linear-Regression.

Panels 3: 3-Way Analysis of Externalizing-Problems 22q11DS and BMI Trajectory.

Panel 3A: Comparison of CBCL/ABCL Externalizing-Problems-T-Score trajectory across Healthy Controls (in Green) and 22q11DS individuals divided in High Externalizing-Problems (in Brown) and Low Externalizing-Problems (in Yellow) according to lifetime T-Scores > 55.

Panel 3B: Comparison of BMI trajectory across Healthy Controls (in Green) and 22q11DS individuals divided in High Externalizing-Problems (in Brown) and Low Externalizing-Problems (in Yellow) according to lifetime T-Scores > 55.

Panel 3C: Mediation analysis between 22q11DS diagnosis by age (input), Externalizing Problems diagnosis by age (mediator) and BMI trajectory (outcome).

Panel 4: Comparison of BMI trajectory across 22q11DS individuals with High Externalizing Problems divided according to lifetime prescription of psychostimulant medication. No-Psychostimulant-Males in dark blue, No-Psychostimulant-Females in red, Psychostimulant-Males in light blue, and Psychostimulant-Females in orange.

Figure 3:

Downstream clinical and neurodevelopmental consequences of atypical BMI trajectories emerging during longitudinal follow-up.

Panels 1A-1D: Differential vulnerability to depression during longitudinal follow-up in Increasing-vs-Decreasing-BMI-Trajectory Subgroups. Increasing-BMI-Males in dark blue, Increasing-BMI-Females in red, Decreasing-BMI-Males in light blue, and Decreasing-BMI-Females in orange.

Panel 1A: Kaplan-Meyer survival curves for lifetime Depressive Disorder across BMI-Trajectory Subgroups.

Panel 1B: Severity of the Dysphoric-Mood item of the SIPS compared across BMI-Trajectory Subgroups with Mixed-Model-Linear-Regression.

Panel 1C: Severity of the Depression item of the BPRS compared across BMI-Trajectory Subgroups with Mixed-Model-Linear-Regression.

Panel 1D: Severity of the Excessive Guilt item of the BPRS compared across BMI-Trajectory Subgroups with Mixed-Model-Linear-Regression.

Journal Pre-proof

Panels 2A-2D: Differential vulnerability to psychotic disorders during longitudinal follow-up in High-vs-Low-Baseline-BMI-Subgroups. High-Baseline BMI-Males in dark blue, High-Baseline-BMI-Females in red, Low-Baseline-BMI-Males in light blue, and Low-Baseline-BMI-Females in orange.

Panel 2A: Kaplan-Meyer survival curves for lifetime Psychotic Disorder across Baseline-BMI Subgroups.

Panel 2B: Severity of the Bizarre-Thinking item of the SIPS compared across Baseline-BMI-Subgroups with Mixed-Model-Linear-Regression. In the left portion of the panel symptom severity is modelled according to age while in the middle portion it is modelled according to time after baseline assessment. The right most portion captures mediation analysis between Baseline-BMI-Group by age (input), Baseline-BMI-Group by time after baseline assessment (mediator) and Bizarre-Thinking Severity (outcome)

Panel 2C: Severity of the Motor-Disturbance item of the SIPS compared across Baseline-BMI-Subgroups with Mixed-Model-Linear-Regression. In the left portion of the panel symptom severity is modelled according to age while in the middle portion it is modelled according to time after baseline assessment. The right most portion captures mediation analysis between Baseline-BMI-Group by age (input), Baseline-BMI-Group by time after baseline assessment (mediator) and Motor-Disturbance Severity (outcome).

Panel 2D: Severity of the BPRS Conceptual Disorganization item compared across Baseline-BMI-Subgroups with Mixed-Model-Linear-Regression. In the left portion of the panel symptom severity is modelled according to age while in the middle portion it is modelled according to time after baseline assessment. The right most portion captures mediation analysis between Baseline-BMI-Group by age (input), Baseline-BMI-Group by time after baseline assessment (mediator) and Motor-Retardation Severity (outcome).

Panels 3: 3-Way analysis of Externalizing-Problems, Baseline-BMI and Psychosis Trajectory. The left plots depict clinical trajectory according to both Externalizing-Problems and Baseline-BMI Diagnosis. High-Baseline-BMI/High-Externalizing-Problems (purple), High-Baseline-BMI/Low-Externalizing-Problems (brown), Low-Baseline-BMI/High-Externalizing-Problems (yellow), Low-Baseline-BMI/Low-Externalizing-Problems (green). The right plots describe mediation analysis between Externalizing-Problems diagnosis by age (input), Baseline-BMI diagnosis by age (input) and psychosis clinical trajectory (outcome).

Panel-3A: Psychotic Disorder Diagnosis.

Panel-3B: SIPS-Bizarre-Thinking severity.

Panel-3C: SIPS-Motor-Disturbance severity.

Panel-3D: BPRS-Motor-Retardation severity.

Panel 4A: Trajectories of Cerebellar Gray Matter Volume (GMV) compared across baseline BMI-Subgroups using Mixed-Model-Linear-Regression, correcting for gender, psychotropic medication, intracranial volume, and scanner type. The upper panel displays the developmental trajectory of posterior-inferior (Crus 1) Gray Matter Volume. High-Baseline-BMI in Purple. Low-Baseline-BMI in Green. The anatomical pattern displays diverging developmental trajectories of 12 cerebellar subfields across subgroups. Subfields are color coded from dark to light blue according to p-value of age-interaction effect (darker blue indicating more significant differences). Subfields with non-significant differences after False Discovery Rate correction for multiple comparisons are displayed in gray.

Panel 4B: Trajectories of Cerebellar Gray Matter Volume (GMV) compared across baseline BMI-Subgroups using Mixed-Model-Linear-Regression, correcting for gender, psychotropic medication, intracranial volume, and scanner type. Cerebellar GMV trajectories are modelled according to time from baseline assessment to characterize to investigate whether divergent cerebellar trajectories across Baseline-BMI subgroups were more directly predicted by duration of High-vs-Low BMI status that by the effect of age.

Panel 4C: Mediation analysis between Baseline-BMI by age (input), Baseline-BMI by Time from Baseline-Assessment (mediator) and posterior-inferior (Crus 1) Gray Matter Volume (outcome).

Panels 5: 3-Way Analysis of Baseline-BMI, Cerebellar Trajectory and Psychosis Trajectory.

Journal Pre-proof

Panel 5A: Multivariate cerebellar pattern, derived from PLCS analysis capturing multivariate association between SIPS symptoms severity and Cerebellar-GMV. Color coding reflects loading of cerebellar lobules on the multivariate pattern, with Blue indicating significant positive loading and Red significant negative loading.

Panel 5B: Multivariate SIPS clinical pattern derived from PLCS analysis capturing multivariate association between SIPS symptoms severity and Cerebellar-GMV. Symptoms highlighted in yellow contribute significantly to the pattern.

Direct of the bar plot reflects direction of association of individual SIPS symptoms (upwards positive association, downwards negative association),

Panel 5C: Association of Multivariate Cerebellar-GMV scores and SIPS-Symptom scores detected from PLCS analysis, modelled using MMLR separately for High-Baseline-BMI subgroup (in purple) and Low-Baseline-BMI subgroup (in yellow).

Panel 5D: Mediation analysis restricted to the High-Baseline-BMI subgroup, between age (input), Cerebellum-GMV score derived from PLS analysis (mediator), and SIPS-Symptom-Score derived from PLS analysis (outcome).

Figure 4:

Schematic representation of a possible developmental pathways accounting for the main results and discussed above.

White boxes highlight correlates of atypical BMI trajectories observed at different developmental stages. **Box 1:** Behavioral impulsivity evident particularly during childhood predicts subsequent alterations in BMI Trajectory. **Box 2:** Deviations in BMI trajectories in 22q11DS emerge during childhood and progressively worsening during adolescence and early adulthood, preceding the prescription of antipsychotic medication. **Box 3:** Atrophy of the Posterior Inferior Cerebellum develops progressively as a result of chronic metabolic dysregulation following a dose-effect relationship with duration of High-BMI Status. **Box 4:** Progressive cerebellar atrophy is linked to the development of motor and cognitive disorganization symptoms that also follow a dose effect relationship with duration of High-BMI status. **Box 5:** Progressive worsening of disorganization symptoms results in increased vulnerability of being diagnosed with a psychotic disorder requiring antipsychotic treatment as a result of chronic metabolic dysregulation.

Gray boxes highlight non-measured mechanisms that could hypothetically link the different developmental alterations. **Box H1:** Impulsive eating patterns could mediate the link between behavioral impulsivity and early chronic BMI increases reflecting shared impairment of cortico-striatal circuits responsible for top-down inhibitory control goal-directed and feeding behavior. **Box H2**: Chronic pro-inflammatory stated linked to prolonged metabolic dysregulation could affect cerebellar maturation and contribute to account for the dose effect relationship linking duration of metabolic dysregulation to progressive cerebellar atrophy. **Box H3:** Alterations in the posterior inferior cerebellum could impair predictive modelling of higher order cognitive processes resulting in motor and cognitive disorganization symptoms of psychosis and progressive worsening of executive and attentional difficulties.

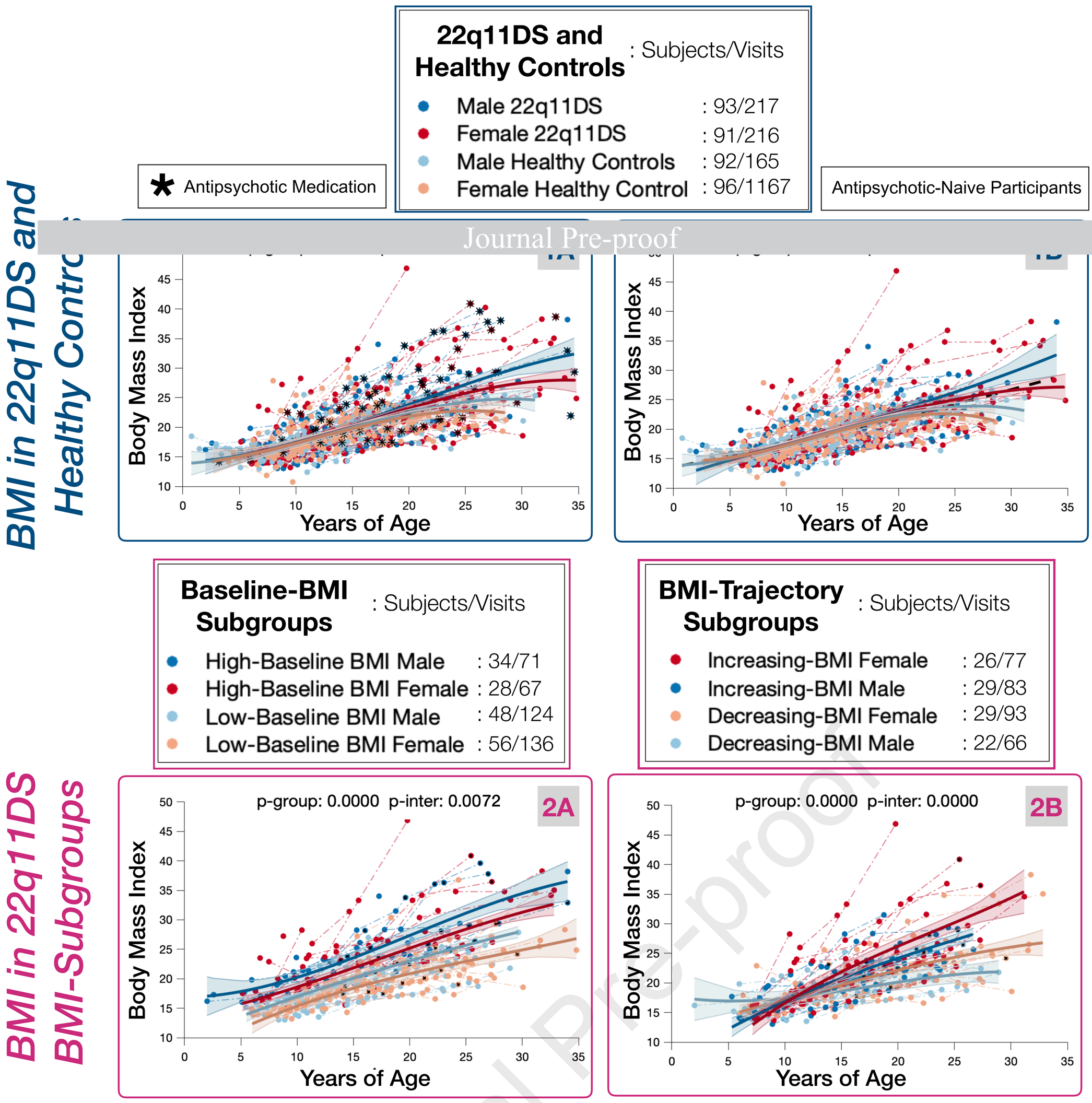
Journal Pre-proof

Journal Pre-proof

Table 1 – Part 1: Demographics Features

		22q11DS	HC	22q11DS-vs-HC p-value	Decreasing-BMI 22q11DS-	Increasing -BMI 22q11DS-Subgroup	Increasing-vs-Decreasing-BMI P-Value	Low-Baseline-BMI 22q11DS-Subgroup	High-Baseline-BMI 22q11DS-	High-vs-Low Baseline-BMI P-Value
Number of Subjets/Assesment		184/433	188/332		51/159	55/160		104/258	62/138	
Number of Assessments per Subject: mean (sd) [1]		2.3(1.2)	1.7(0.85)	<0.001*	3.1(1.1)	2.9(0.9)	0.3	2.4 (1.2)	2.2 (1.1)	0.2
Age: mean(sd)[1]		16.49(6.7)	14.4 (6.7)	<0.001*	17(6.9)	15.7(5.4)	0.06	16.4 (6.3)	16.2 (7.1)	0.82
Baseline Age: mean (sd) [1]		13.2(6.6)	12.9(5.8)	0.66	12.1(5.5)	11.6(3.8)	0.62	13 (6)	12.5 (6.4)	0.66
Age at Last Longitudinal Follow-Up[1]		18.4 (7.6)	15.9 (6)	<0.001*	19.9(7.5)	19.2(5.2)	0.54	18.6(7)	17.4(8.2)	0.33
Duration of Longitudinal Follow-Up: mean (sd) [1]		5.1(4.7)	2.9(3.3)	<0.001*	7.8(4.3)	7.5 (3.7)	0.69	5.6 (4.8)	4.8(4.8)	0.34
Gender(male:female. subjects/visits) [2]		93:91/	92:96/	0.75/0.9	22:29/66:93	29:26/83:77	0.32/0.06	48:56/124:136	34:28/71:67	0.28/0.43
Medication (Subjects/Visits)	**Atypical Antipsychotic[2]**	38/66			10/14	9/13	0.84/0.89	9/14	11/18	0.08/0.008*
	Psychostimulant[2]	83/145			32/52	38/58	0.53/0.34	46/73	26/48	0.67/0.97
	SSRI[2]	49/78			20/28	21/30	0.94/0.81	25/42	17/25	0.62/0.64
Endocrine Disorder (subjects/visits)	**Hypoparathyroidy[2]**	8/184	0/187	0.004*	2/51	3/55	0.71	6/56	2/102	0.02*
	Hypothyroidy[2]	23/184	0/187	<0.0001*	8/51	7/55	0.66	10/52	13/91	0.51
	Diabetes[2]	2/184	3/187	0.67	0/51	1/55	0.33	0/62	1/103	0.44
Socioecomic status: mean (sd)	**Household income[1]**	5.67 (2.43)	6.15 (2.73)	0.17	5.41 (2.44)	5.63 (2.46)	0.67	5.66 (46)	5.57 (2.42)	0.81
	Education[1]	4.92 (1.44)	5.1 (1.42)	0.42	4.56 (1.53)	4.78 (1.13)	0.42	4.73 (1.48)	5.1 (1.38)	0.14

Journal Pre-proof



Journal Pre-proof

Journal Pre-proof

1 Impulsivity in Baseline-BMI Subgroups

2 Impulsivity in BMI-Trajectory Subgroups

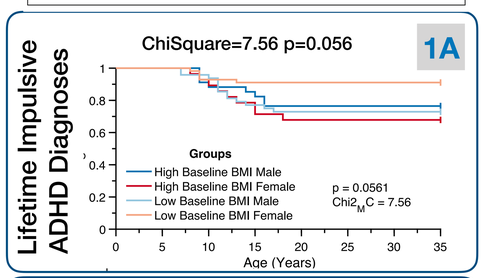
Baseline-BMI Subgroups : Subjects/Visits

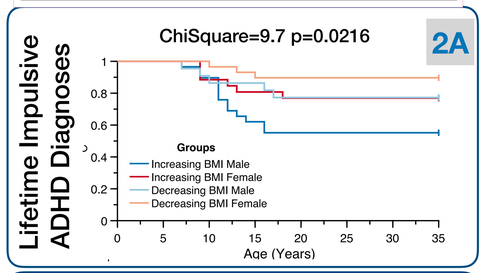
- High-Baseline BMI Male : 34/71
- High-Baseline BMI Female : 28/67
- Low-Baseline BMI Male : 48/124
- Low-Baseline BMI Female : 56/136

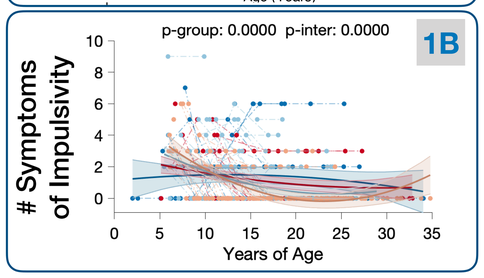
BMI-Trajectory Subgroups : Subjects/Visits

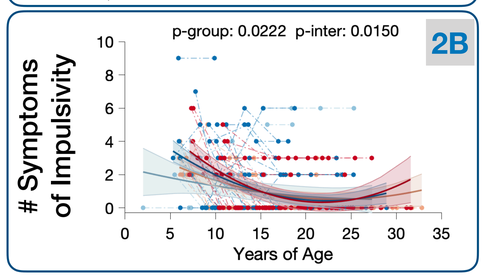
- Increasing-BMI Female : 26/77
- Increasing-BMI Male : 29/83
- Decreasing-BMI Female : 29/93
- Decreasing-BMI Male : 22/66

DSM-5 Symptoms of Impulsivity

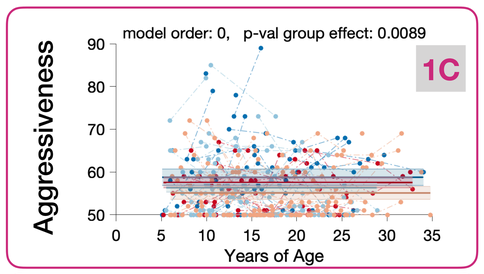


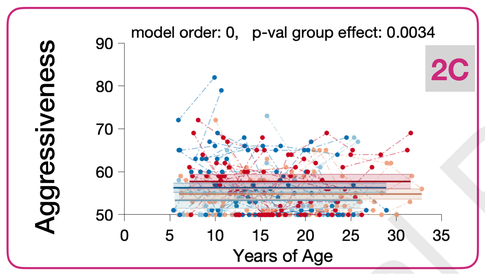


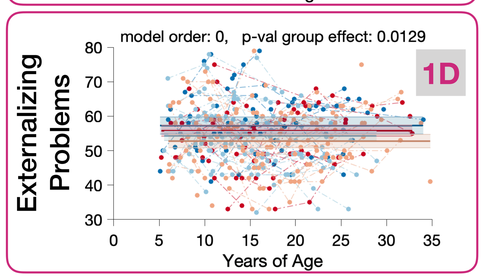


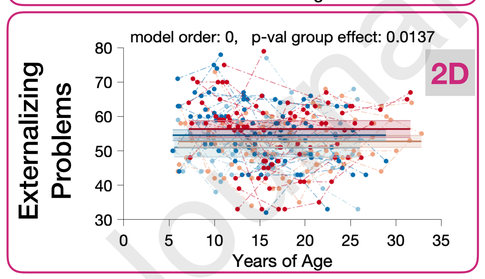


CBCL Behavioral Impulsivity

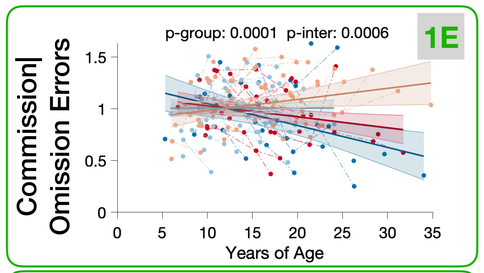


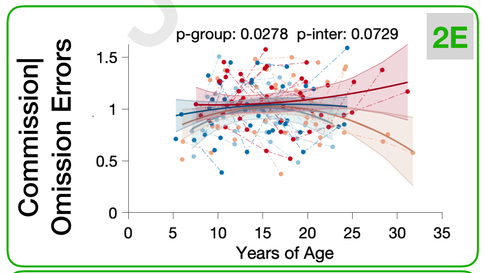


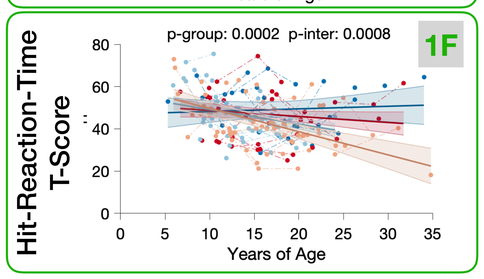


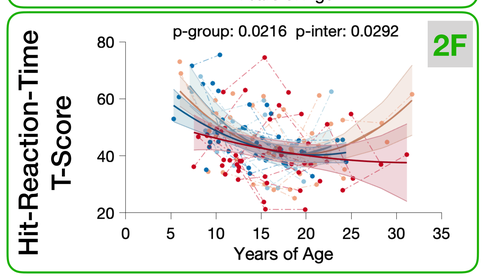


CPT2 Neurocognitive Impulsivity





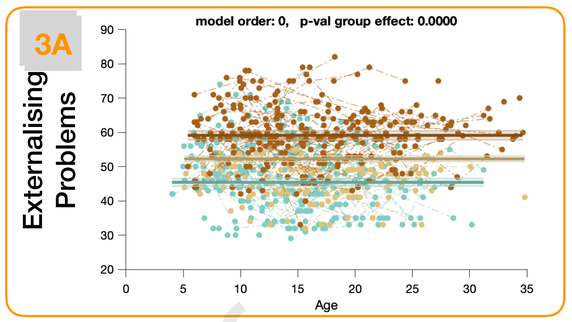


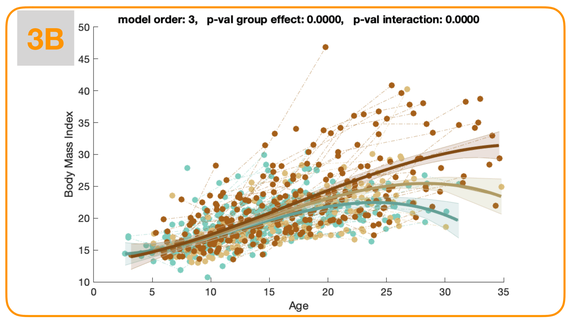


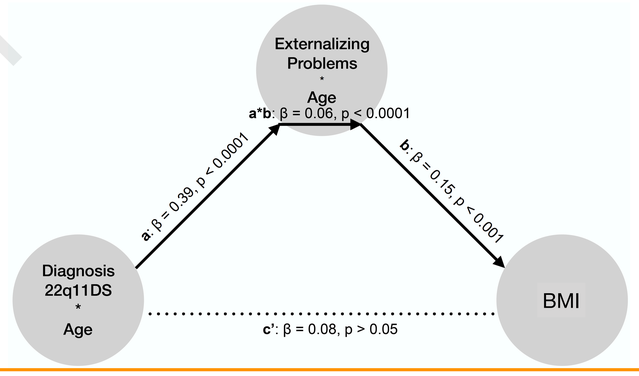
3 3-Way Analysis of Externalizing-Problems, 22q11DS and BMI Trajectory

Externalizing Problems Subgroups

- Ext+ 22q11DS : 115/286
- Ext- 22q11DS : 65/142
- HC : 178/320



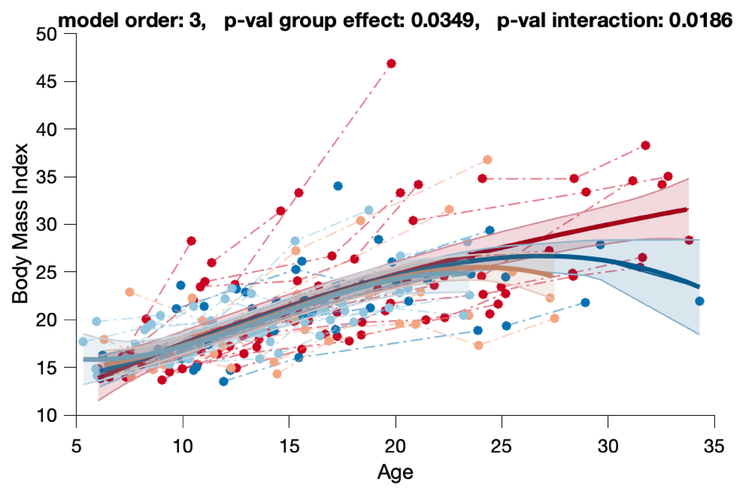




4 Effect of Psychostimulant Medication on atypical BMI Trajectory in 22q11DS with High-Externalizing Problems

22q11DS - Externalizing Problems Subgroups

- Ext+ Psychostimulant- Female : 36/84
- Ext+ Psychostimulant- Male : 29/43
- Ext+ Psychostimulant+ Female : 13/36
- Ext+ Psychostimulant+ Male : 24/61

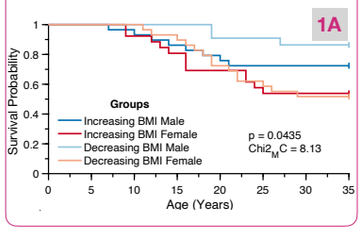


1 Depression Trajectory in BMI-Trajectory Subgroups

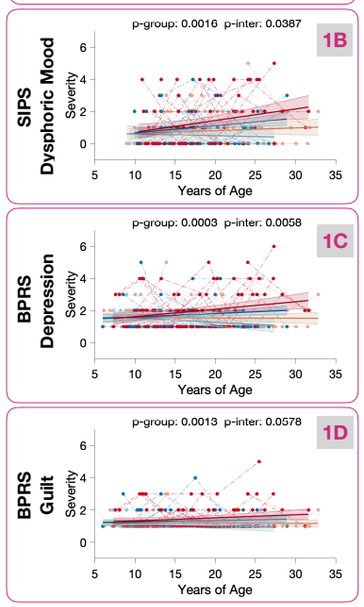
BMI-Trajectory Subgroups : Subjects/Visits

- Increasing-BMI Female : 26/77
- Increasing-BMI Male : 29/83
- Decreasing-BMI Female : 29/93
- Decreasing-BMI Male : 22/66

Lifetime Depressive Disorder According to BMI-Trajectory



Trajectory According to Age and BMI-Trajectory

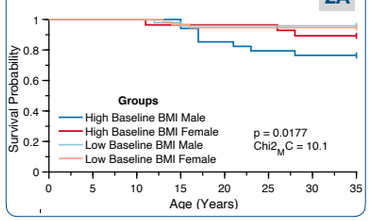


2 Psychosis Trajectory in Baseline-BMI Subgroups

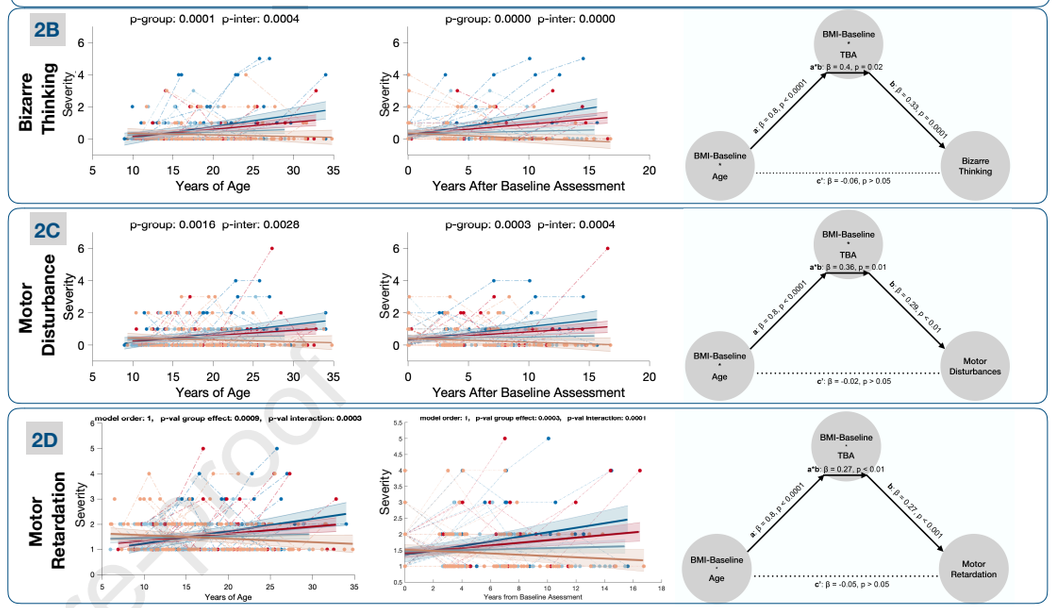
Baseline-BMI Subgroups : Subjects/Visits

- High-Baseline BMI Male : 34/71
- High-Baseline BMI Female : 28/67
- Low-Baseline BMI Male : 48/124
- Low-Baseline BMI Female : 56/136

Lifetime Psychotic Disorder According to Baseline-BMI



Trajectory According to Age and Baseline BMI | *Trajectory According to Time from Baseline Assessment (TBA)* | *3-Way Mediation Analysis of Age, TBA and Symptom Severity*

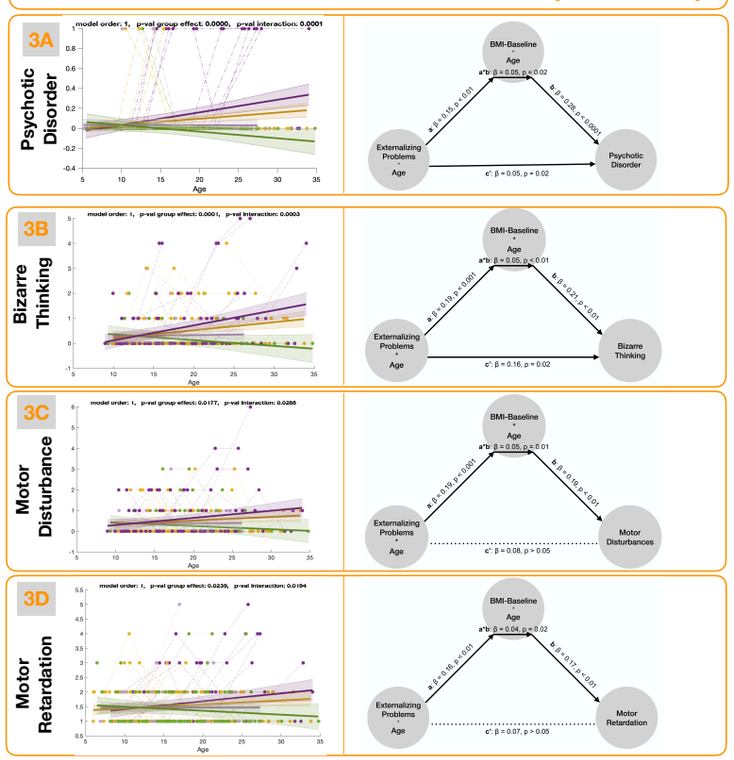


3 3-Way Analysis of Externalizing-Problems, Baseline-BMI and PsychosisTrajectory

Externalizing Problems Subgroups : Subjects/Visits

- Ext+ High-Baseline BMI : 38/94
- Ext+ Low-Baseline BMI : 60/157
- Ext- High-Baseline BMI : 20/ 39
- Ext- Low-Baseline BMI : 44/101

Trajectory According to Age, Externalizing-Problems and Baseline-BMI | *3-Way Mediation Analysis of Externalizing-Problems, Baseline-BMI and Psychosis Severity*

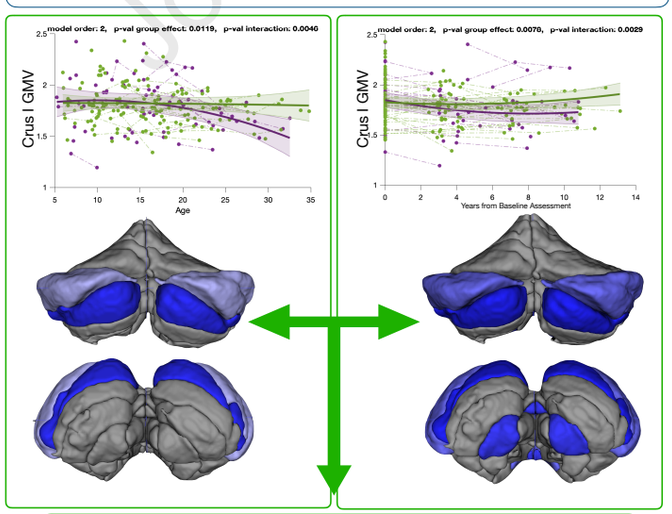


4 Cerebellar Trajectory in Baseline-BMI Subgroups

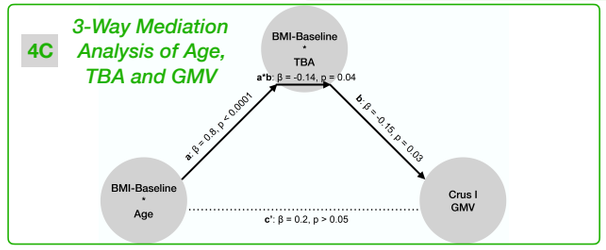
Baseline-BMI Subgroups : Subjects/Visits

- High-Baseline-BMI : 42/71
- Low-Baseline-BMI : 80/156

4A Trajectory According to Age and Baseline BMI | *4B Trajectory According to Time from Baseline Assessment (TBA)*

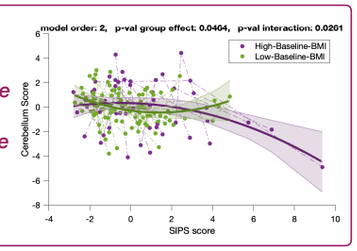


4C 3-Way Mediation Analysis of Age, TBA and GMV

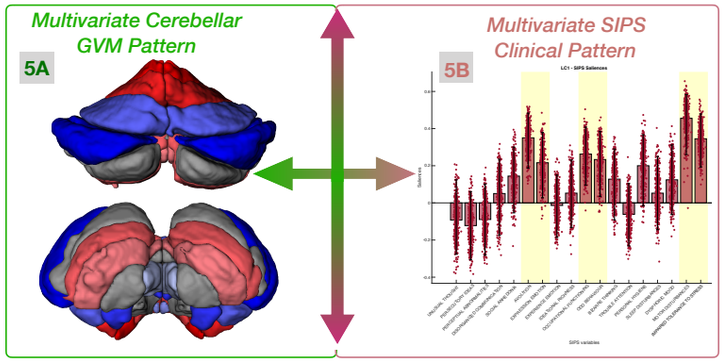


5 3-Way Analysis of Baseline-BMI, Cerebellar Trajectory and Psychosis Trajectory

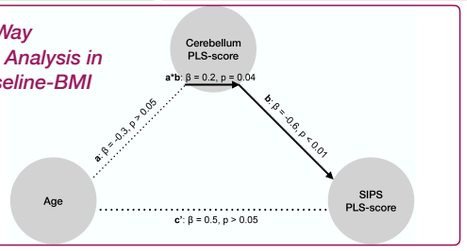
5C Correlation of Cerebellar-GVM Score and SIPS-Symptom-Score Moderated by Baseline-BMI

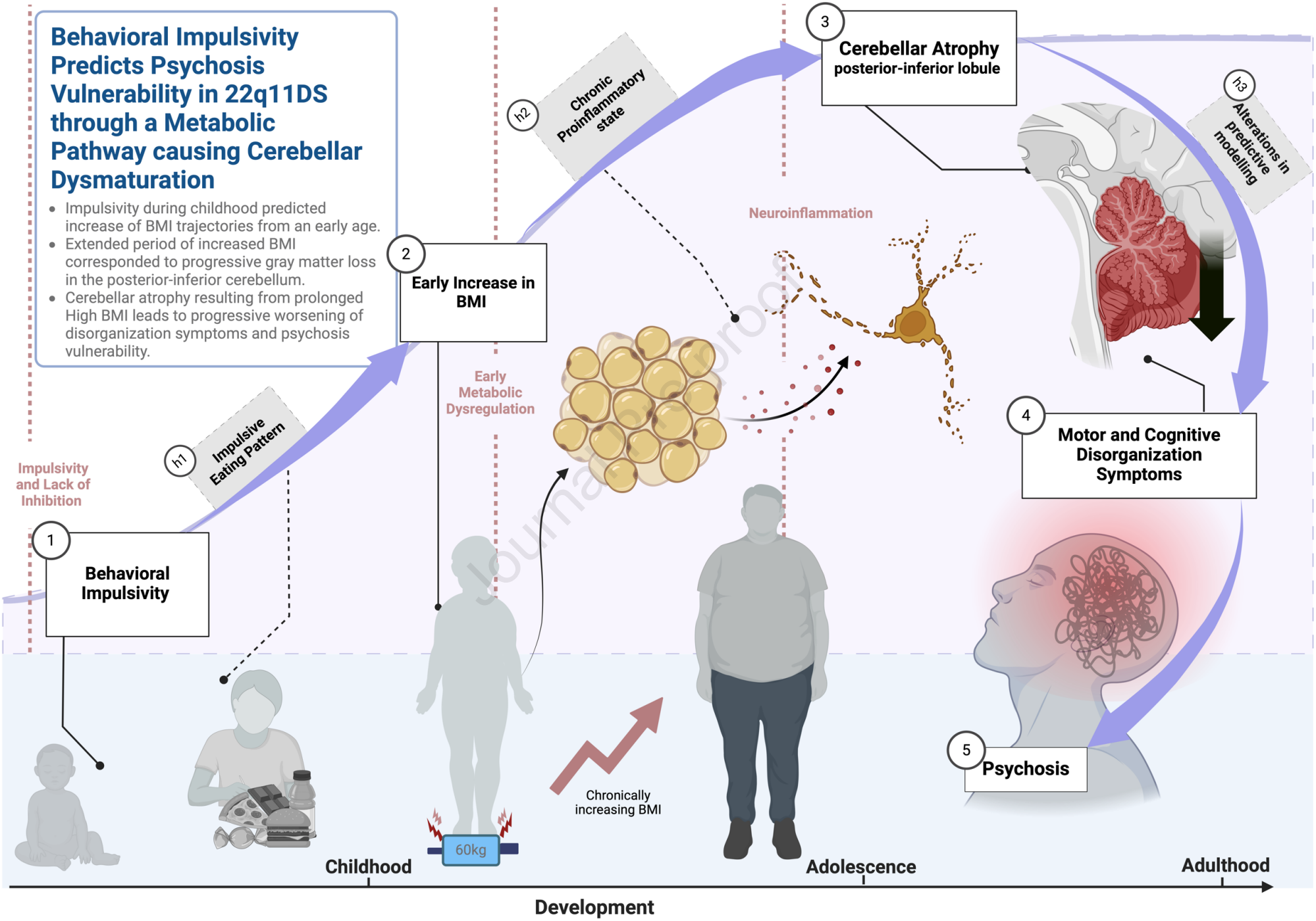


Multivariate Cerebellar GVM Pattern | *Multivariate SIPS Clinical Pattern*



5D 3-Way Mediation Analysis in High-Baseline-BMI



Journal Pre-proof

Journal Pre-proof