

BMJ Open Rationale and design of GENEiUS: a prospective observational study on the genetic and environmental determinants of body mass index evolution in Canadian undergraduate students

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ABSTRACT

Introduction Obesity is a global epidemic and is a risk factor for developing other comorbidities. Young adulthood is a critical period for body weight change and establishing healthy lifestyle behaviours. The 'Freshman 15' suggests that undergraduate students gain 15 lbs (6.8 kg) during their first year of university, although evidence estimates a more modest weight gain of approximately 3–5 lbs (1.4–2.3 kg). Previous studies have only investigated weight change in the first year and do not study potential risk factors. Genetic and Environmental Effects on weight in University Students (GENEiUS) is a prospective observational study which will investigate the environmental and biological determinants of weight change in undergraduate students over 4 years.

Methods and analysis The GENEiUS study will recruit 2500 multiethnic undergraduates aged 17–25 years at McMaster University at the start of their first year and will follow them every 6 months for 4 years. Primary outcomes are obesity traits: body mass index, waist circumference, waist-to-hip ratio, body fat mass and body fat percentage. The contribution of well-established and novel genetic variants for obesity traits and heritability values will be derived from whole-genome single-nucleotide polymorphism genotyping arrays. Civil status, age, sex, ethnicity, length of residence in Canada, religiosity, energy intake, physical activity, exercise motivation, electronic screen time, sleep patterns, history of assault, smoking status, alcohol consumption, medication and drug use, stress, impulsivity, body image perception, self-esteem, anxiety, eating disorders and depression will be investigated for their effect on obesity traits. The findings of the GENEiUS study will be used to help design obesity prevention programme in North American universities with multiethnic populations.

Ethics and dissemination Ethical approval of the study protocol has been obtained from the Hamilton Integrated Research Ethics Board. Study results will be disseminated through scientific publications, scholarly meetings, and collaborative meetings with university administration and student groups.

Strengths and limitations of this study

- This is the first adequately powered study to investigate genetic associations of weight change in undergraduate students.
- This is the first study to investigate an exhaustive number of potential risk factors for weight change in undergraduate students.
- While most studies investigating weight changes in undergraduates have taken place over 6–8 months, this study will follow students throughout their studies for 4 years.
- Validated questionnaires will be used to measure the majority of parameters in order to decrease participant burden and limit cost.
- This study is sufficiently powered to identify genetic and environmental predictors of weight change in undergraduate students; however, it is not powered to assess gene–environment interactions.

INTRODUCTION

Obesity in young adulthood

Obesity has become a global epidemic and affects one in five adults in Canada.^{1,2} This is of great concern to public health as obesity is a major risk factor for depression, osteoarthritis, type II diabetes, hypertension, cardiovascular disease and some cancers.^{3,4} The high prevalence, associated comorbidities and increased mortality make obesity a monumental economic burden accounting for \$7.1 billion in Canadian healthcare costs.⁵ Adolescence and young adulthood may be critical periods for the development of obesity as elevated body mass index (BMI) during this time is associated with obesity later in adulthood.⁶ When comparing the prevalence of obesity in Canadian adults from 2010 to 2014, the largest increase was

observed among individuals aged 18–19 years.⁷ While education status is negatively correlated with BMI in the general population from high-income countries, young adults with higher education gain more weight and are more likely to be obese than those without university education in the USA.^{8–10}

The 'Freshman 15' is a popular theory which suggests that university undergraduate students gain 15 lbs (6.8 kg) during their first year of postsecondary education, although the average weight gain is estimated to be 3–5 lbs (1.4–2.3 kg).^{11–13} It should be noted that these studies are limited by small sample sizes, high female-to-male ratios, and may be susceptible to volunteer bias due to high dropout rates. Furthermore, sex-specific and ethnicity-specific subgroup analyses are scarce. Most studies are also only conducted over 1 year and there are limited and conflicting reports over weight change afterward. While one study suggests that students gain weight consistently, another describes stabilisation after the first year of undergraduate education.^{14 15} Overall, students tend to weigh more in the fourth year compared with the first year and it is unclear whether this can be attributed to continued physical development and maturation or the accumulation of fat mass.^{16 17} The entire duration of undergraduate studies may therefore be a critical period for weight change in young adults and this study will provide insight into the genetic and environmental determinants of weight change among this population.

Predictors of undergraduate weight change

The aetiology of obesity is complex and depends on a variety of biological, environmental, lifestyle and socio-economic factors.^{18 19} There is limited evidence on factors influencing weight in undergraduate students. Excessive consumption of calorie-dense foods, the number of meals consumed during the evening and weekends and recent dieting have all been associated with weight gain in undergraduate students.^{20–22} Evidence suggests that a lack of healthy food options on campus and buffet-style meal plan design may facilitate the development of unhealthy eating patterns among students.^{23 24} Further, the increased expenses of university tuition and living away from home limit a student's budget to purchase healthy foods which often cost more.^{23 24} First year students tend to make unhealthier food choices and increase alcohol consumption as each academic semester progresses, especially near examination time.^{25–28} These poor eating habits coupled with decreased physical activity and increased sedentary behaviour from internet usage may partially explain the mean weight gain of 3–5 pounds in the first year.²⁹ Their low motivation to exercise may also be detrimental as greater motivation promotes weight loss in both the short and long term.^{24 30}

Undergraduate students sleep less and more erratically than high school students.²⁷ Sleep and BMI have a U-shaped relationship such that short and long sleep durations are associated with elevated BMI.³¹ In undergraduates, a decrease in the quantity but not the quality

of sleep is related to weight gain.²⁰ Students are also subject to greater stress as they transition to undergraduate studies due to an increased academic workload and by living away from home and away from social support systems. Stress has previously been associated with both weight gain and weight loss in undergraduate students.²⁸ Interestingly, BMI may moderate the effect of stress on weight change in students as high stress has been associated with weight gain among those with high baseline BMI and weight loss in those with low baseline BMI.³² Weight may also be influenced by adverse experiences. History of sexual assault has been linked to obesity and elevated BMI in some studies.^{33 34} This is of particular concern to university students as 14%–44% report experiencing some form of sexual assault since starting undergraduate studies.³⁵

Undergraduate students have described lack of self-control as a barrier to making healthy dietary choices.²³ Impulsivity in the context of weight maintenance, as measured by delayed discounting, reflects preferences for small immediate pleasures compared with larger rewards later in life. Steeper delayed discounting, indicating more impulsive choices, has been associated with obesity, especially in adolescents.³⁶ Further, impulsive personality traits have been positively associated with BMI in university students indirectly through compulsive eating behaviours.³⁷

Psychiatric conditions may also impact the weight of undergraduate students. Bulimia nervosa and binge eating disorder have been associated with elevated BMI.³⁸ Young adults are especially at risk for pathological eating since the prevalence of eating disorders appears to increase from 0.3% in adolescence to 1% in young adulthood.³⁹ Although there is weak evidence, disordered eating habits have been associated with overweight and obesity in university students.⁴⁰ Further, among female but not male students, weight gain has been associated with greater disordered eating behaviour over 4 years.¹⁴ Both depression and anxiety have been associated with obesity.^{4 41} These conditions are of major concern on university campuses since it is estimated that 18.3% and 14.7% of Canadian students have anxiety and depression, respectively.⁴² Limited studies show that depression appears to be associated with obesity in male, but not female, undergraduate students.^{14 43} Finally, other psychological factors including body image dissatisfaction and low self-esteem have been associated with overweight and obesity in adolescents.⁴⁴ Few studies have investigated these in undergraduate students, and there are conflicting reports whether they are related to weight change.^{45 46}

Among those aged 15–24 years in Canada, approximately 71% report a religious affiliation.⁴⁷ Religiosity has been associated with healthy lifestyle behaviours in adolescents.⁴⁸ While religiosity has been shown to have protective effects on cardiometabolic traits like diabetes and hypertension, it has been associated with elevated BMI.^{49 50} One study found increased incidence of obesity

in religious young adults.⁵¹ Therefore, the effect of religiosity on weight in undergraduates warrants further investigation. Further, birthplace and length of residence may also contribute to weight change in undergraduate students. In the USA, foreign-born immigrants tend to have lower BMI than those born in the USA, yet experience an increase in BMI with length of residence.⁵²

Genome-wide association studies (GWAS) have identified many single-nucleotide polymorphisms (SNPs) associated with BMI, waist-to-hip ratio (WHR) and body fat percentage (%BF); however, these markers are not specific to university students.^{53–55} To the best of our knowledge, only one study from the UK has explored the genetic causes of weight gain in university. It found that *FTO* SNP rs9939609, the most important genetic contributor to obesity in European populations, showed a nominal association with weight gain at the end of the first academic year.⁵⁶ However, the study suffered from several limitations: high dropout rate (78%), low statistical power (n=310) and limited follow-up duration.

To design effective obesity prevention programme in universities, a better understanding of its causes in undergraduate students is needed. The Genetic and Environmental Effects on weight in University Students (GENEiUS) study will investigate the genetic and environmental determinants of obesity trait evolution in undergraduate students at McMaster University (Hamilton, Ontario, Canada) over the 4-year course of their studies.

Study objectives

The primary objectives of this study are to (1) describe BMI level and change over 4 years, (2) investigate the heritability and genetic determinants of BMI level and change and (3) investigate the social, cultural, lifestyle and environmental determinants of BMI level and change in undergraduate students. Secondary objectives of the GENEiUS study include the investigation of genetic and environmental determinants of additional obesity traits (waist circumference, WHR, %BF and body fat mass) and endophenotypes.

METHODS AND STUDY DESIGN

Participant selection and recruitment

The GENEiUS study is a longitudinal prospective observational study in Hamilton, Ontario. Undergraduate students from McMaster University will be followed every 6 months over 4 years beginning in September of their first year of study. First year students enrolled at McMaster University between the ages of 17 and 25 years are eligible to participate in the study.⁵⁷ Individuals who are pregnant, have given birth or have a medical condition which can impact BMI for a long period of time (eg, bariatric surgery, immobilisation from injury, etc) will be excluded from the study.

Beginning in September 2015, first year students are invited to participate from September and October of each year. Recruitment will be conducted via advertising

through presentations, information tables, posters, flyers and social media. Interested students will be given detailed information about the study in person, via email or by phone. Approximately 500 participants will be recruited per year for about 5 years until a goal of 2500 participants is reached. Students will be evaluated for eligibility to participate at the baseline visit and provide informed consent prior to enrolment. Participants will be reimbursed with a gift card on completion of each study appointment.

Data collection

Participants will be assessed every 6 months for 4 years, once in September or October and again in March or April of each academic year (table 1). At the baseline visit only, a saliva sample will be obtained in addition to information on age, sex, ethnicity, birthplace and country of residence history. Weight, height, waist circumference (WC), hip circumference (HC), %BF and body fat mass (BFM) will be measured at baseline and all follow-up appointments. Socioeconomic status, civil status, sexual orientation, medical history, medication and drug use, smoking status, energy intake, meal plan type, alcohol consumption, physical activity, electronic screen time, method commuting to campus, living status on or off campus, sleep health, stress, history of abuse, impulsivity, eating disorders, body dissatisfaction, self-esteem, depression, anxiety and religiosity will be measured at all time-points using online, self-reported questionnaires. Participants will complete their questionnaires and one food recall at their baseline visit with instruction from a research assistant. After receiving this initial training, follow-up questionnaires and food recalls will be completed online outside of study appointments at the participant's leisure to minimise burden. All questionnaires and food recalls will be completed within 3 weeks of a participant's study appointment.

Outcomes

The obesity trait outcome variables are BMI, WC, WHR, %BF and BFM. Trained research personnel will perform all anthropometric measurements in duplicate to reduce intrarater variability. Participants will wear light clothing and remove shoes before being weighed. Weight will be measured to the nearest 0.1 kg using a digital scale (Seca, Hamburg, Germany). Height will be measured to the nearest 0.1 cm using a portable stadiometer (Seca 225, Hamburg, Germany). WC will be measured after a normal exhalation at the midpoint of the last palpable rib and the superior portion of the iliac crest to the nearest 0.1 cm and HC will be measured at the widest part of the buttocks to the nearest 0.1 cm using a stretch-resistant tape measure, as previously described by the WHO.⁵⁸ WHR will be calculated as WC divided by HC. BMI (kg/m²) will be calculated by dividing weight by squared height. Bioelectric impedance analysis (BIA) will be used to assess BFM to the nearest 0.1 kg and %BF to the nearest 0.1%. Participants will remove jewellery before stepping

Table 1 Study timeline, outcomes risk factor variables and measurements

Measurement	September- October Year 1	March- April Year 1	September- October Year 2	March- April Year 2	September- October Year 3	March- April Year 3	September- October Year 4	March- April Year 4
Anthropometric outcomes								
Informed consent	X							
Weight	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X
Waist circumference	X	X	X	X	X	X	X	X
Hip circumference	X	X	X	X	X	X	X	X
BMI	X	X	X	X	X	X	X	X
WHR	X	X	X	X	X	X	X	X
BFM	X	X	X	X	X	X	X	X
%BF	X	X	X	X	X	X	X	X
Genetic factors								
DNA sample	X							
Cultural, environmental, lifestyle and social factors								
Age, sex, ethnicity	X							
Birthplace, changes in country of residence	X							
Sexual orientation, civil status	X	X	X	X	X	X	X	X
Socioeconomic status	X	X	X	X	X	X	X	X
Meal plan type	X	X	X	X	X	X	X	X
Commuting method	X	X	X	X	X	X	X	X
Living status on/off campus	X	X	X	X	X	X	X	X
Medical history	X	X	X	X	X	X	X	X
Medication and drug use	X	X	X	X	X	X	X	X
Smoking history	X	X	X	X	X	X	X	X
Time using electronic devices	X	X	X	X	X	X	X	X
Energy intake	X	X	X	X	X	X	X	X
Alcohol consumption	X	X	X	X	X	X	X	X
Physical activity	X	X	X	X	X	X	X	X
Exercise motivation	X	X	X	X	X	X	X	X

Continued

Table 1 Continued

Measurement	September- October Year 1		March- April Year 1		September- October Year 2		March- April Year 2		September- October Year 3		March- April Year 3		September- October Year 4		March- April Year 4	
Sleep health	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stress	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
History of assault	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Impulsive personality traits	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Impulsive choice	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Eating disorders	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body dissatisfaction	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-esteem	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Depression	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anxiety	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Religiosity	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X

%BF, body fat percentage; ASA24, Automated Self-Administered 24 hours; AUDIT, Alcohol Use Disorders Identification Test; BFM, body fat mass; BIA, bioelectric impedance analysis; BMI, body mass index; BREQ-2, Exercise Regulations Questionnaire; BSQ-8C, 8-item Body Shape Questionnaire; CESD-R, Centre for Epidemiologic Studies Depression Scale Revised; DDT, delay discounting task; DUREL, Duke University Religion Index; EDDS, Eating Disorder Diagnostic Scale; GAD-7, 7-item Generalised Anxiety Disorder Scale; GPAQ, Global Physical Activity Questionnaire; PSQI, Pittsburg Sleep Quality Index; SPAQ, Sexual and Physical Abuse Questionnaire; SUPPS-P, Short Impulsive Behaviour Scale; WHR, waist-to-hip ratio.

barefoot onto the BIA device (Tanita SC-331S, Arlington Heights, Illinois, USA).

Predictor variables

A variety of genetic and environmental predictors of weight will be measured. Potential risk factors for obesity including age, sex, ethnicity, socioeconomic status, civil status, sexual orientation, smoking status, medical conditions, medication or drug use, living status on or off campus, method of commuting to campus, meal plan type (of the several meal plan choices offered both on and off residence), time spent using electronic devices, birthplace and history of country residence will be evaluated through online, self-reported questionnaires.

DNA extraction, whole-genome genotyping and whole-exome sequencing

DNA will be collected from a saliva sample. Saliva will be collected and preserved using the Norgen saliva collection kit (RU4500, Norgen Biotek Corporation, Thorlord, Canada) as per the manufacturer's instructions and stored at room temperature. Before purification, saliva samples will be incubated overnight at 50°C. DNA will be purified from 4mL of preserved saliva using the Chemagen 500 MSM I (PerkinElmer chemagen Technologie GmbH, Baesweiler, Germany) as per the manufacturer's instructions. Two types of genetic experiments will be performed in the present study using Illumina microarray genotyping and next-generation sequencing platforms at the McMaster Genome Facility. Genotyping of whole-genome SNP arrays for each participant will be done to study the association of common and low-frequency genetic variants (minor allele frequency >0.005) with obesity traits. We plan to use the Illumina Infinium Multi-Ethnic Global-8 microarray because it combines a relatively high density of SNPs (1.7 million) with an SNP tagging strategy adapted to ethnically diverse populations. Whole-exome sequencing (WES) will be used to study the association of rare coding variants with obesity traits. WES will be performed on a subset of participants who have extreme decreases in BMI (≤ 10 th percentile), maintain BMI (45th to 55th percentile) and extreme increases in BMI (≥ 90 th percentile) between baseline and 1 year post baseline. We also plan to use the Illumina TrueSeq Exome kit for DNA library preparation and HiSeq 1500 for DNA sequencing, as per the manufacturer's instructions.

Energy intake

Energy intake will be assessed with a 3-day 24-hour food recall, which was selected for its validity, reliability and minimal participant burden.⁵⁹ Participants will recall their energy intake from 2 weekdays and 1 weekend day using the 2016 Canadian adaptation of the Automated Self-Administered 24-hour Recall.⁶⁰ Three-day total energy intake will be averaged to give a mean value per day in kcal. Values for nutrient intake including total carbohydrates (g), protein (g) and fats (g), including

saturated fat, monounsaturated fat and polyunsaturated fat will be reported.

Alcohol consumption

The self-reported version of the Alcohol Use Disorders Identification Test (AUDIT) will be used as a validated measure of alcohol consumption.⁶¹ The AUDIT is a 10-item questionnaire with each question rated on a 5-point scale from 0 to 4 and summed to give a total global score out of 40. Higher scores indicate greater risk of dangerous drinking habits. A score of 8 or more indicates harmful alcohol use with possible alcohol dependence.

Physical activity

Physical activity will be assessed using a 16-item, self-reported version of the Global Physical Activity Questionnaire (GPAQ). The GPAQ was selected for its use in broad populations and its ability to assess physical activity and sedentary time at work, for recreation and during transportation.⁶² Although the GPAQ is traditionally delivered in-person or via telephone interview, self-reported administration has been shown to be a comparable alternative and the self-reported version will be used in this study for its feasibility.⁶³ The GPAQ will be scored by calculating Total Metabolic Equivalent of Task minutes per week as previously described by the WHO.⁶⁴

Exercise motivation

The exercise regulations questionnaire is a 19-item, self-reported questionnaire which measures motivation towards exercising in five domains: external regulation, intrinsic regulation, identification, introjection and motivation.⁶⁵ Each item is scored on a 5-point scale from 0 (*not true for me*) to 4 (*very true for me*). The mean score of each subscale will be calculated and used in analysis. Higher scores indicate greater motivation.

Sleep

Sleep health will be measured by the Pittsburgh Sleep Quality Index (PSQI) as a reliable measure for sleep quality in university students.^{66 67} The PSQI is a 24-item, self-reported questionnaire which measures seven domains of sleep health over the past month: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction. Each domain is scored on a 4-point scale from 0 (*not during the past month*) to 3 (*three or more times per week*) and summed to give a total global score out of 21. Higher scores indicate poorer sleep quality.

Stress

Hair cortisol concentration (pg/mg) will be measured as a biochemical marker for exposure to physical stressors and ongoing chronic stress.⁶⁸ Hair strands will be cut as close to the scalp as possible from the posterior vertex position. At least 10mg of hair from the most proximal 3cm, representing the last 3 months of hair growth, will be analysed.⁶⁹ Cortisol will be extracted as previously described and measured using ELISA.⁷⁰

History of abuse

The Sexual and Physical Abuse Questionnaire (SPAQ) is a 9-item, self-reported questionnaire and will be used as a validated measure of physical and sexual abuse.⁷¹ It assesses abuse at four time points: (1) <6 years old, (2) >6 but <12 years old, (3) >12 but <16 years old and (4) >16 years old. Positive answers indicate a history of abuse. Due to the potentially triggering nature of this questionnaire, participants will be provided with contact information for local legal and support resources at the time of data collection.

Impulsivity

To measure impulsive personality traits, the Short UPPS-P Impulsive Behaviour Scale will be used and was selected for its use in university students.^{72 73} It is a 20-item, self-reported questionnaire with subscales to measure negative urgency, positive urgency, lack of perseverance, lack of premeditation and sensation seeking. Items are scored on a 4-point scale from 1 (*strongly agree*) to 4 (*strongly disagree*) with higher scores indicating more impulsive behaviour. Mean scores from each subscale will be calculated and summed to give a total global score from 5 to 20.

A computer-administered delay discounting task (DDT) will be used to measure impulsive choice.⁷⁴ This is a 5-item task, whereby participants are asked to choose between an immediate reward of \$100 or a delayed reward of \$1000. Monetary values will be held constant, while temporal delays will be adjusted up or down, ranging from 1 hour to 25 years, depending on the choice made by each participant. This task will result in 32 potential Effective Delay 50% (ED₅₀) scores approximately evenly spaced on a logarithmic scale. Temporal discounting rates, *k* values, will be generated for each participant by calculating the inverse of ED₅₀. Higher *k* values reflect greater impulsivity.

Eating disorders

Eating disorders will be evaluated using the Eating Disorder Diagnostic Scale (EDDS) developed for use in community populations.⁷⁵ The EDDS is a 22-item, self-reported questionnaire which assesses Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for diagnosing anorexia nervosa, bulimia nervosa and binge-eating disorder in respondents. It will be scored as previously described.⁷⁵ Scores will be analysed dichotomously by eating disorder diagnosis and continuously by total global score.

Body dissatisfaction

Concern about body image will be measured using the 8-item Body Shape Questionnaire (BSQ-8C) for its use in community populations.^{76 77} The BSQ-8 is a self-reported questionnaire which assesses body shape concerns over the last 4 weeks on a 6-point scale from 1 (*never*) to 6 (*always*). Higher scores indicate greater body dissatisfaction.

Self-esteem

Self-worth will be measured using the Rosenberg self-esteem scale for its wide use in general populations.⁷⁸ It is

a self-reported questionnaire which measures self-esteem on a 4-point scale from 1 (*strongly disagree*) to 4 (*strongly agree*). Higher scores indicate higher self-esteem.

Depression

Depressive symptoms will be evaluated by the Centre for Epidemiological Studies Depression Scale Revised (CESD-R) for its validated use in university students.^{79 80} The CESD-R is a 20-item, self-reported questionnaire with subscales to measure sadness, loss of interest, appetite, sleep, thinking and concentration, guilt, fatigue, agitation and suicidal ideation during the past week. The CESD-R is scored using a frequency 5-point scale for each item from 0 (*not at all or less than 1 day*) to 4 (*nearly every day for 2 weeks*). Higher scores indicate greater depressive symptoms. A cumulative score of at least 16 out of 60 indicates risk of clinical depression. A major depressive episode is characterised by loss of interest or sadness nearly every day for the past 2 weeks, and symptoms in another four DSM symptom groups occurring nearly every day for the past 2 weeks.

Anxiety

The 7-item Generalised Anxiety Disorder Scale (GAD-7) is a valid measure of anxiety.⁸¹ The GAD-7 is a self-reported questionnaire which assesses anxious symptoms in the last 2 weeks on a 4-point scale from 0 (*Not at all*) to 3 (*Nearly every day*). Higher scores indicate greater anxiety. Scores of 10 or greater indicate risk of an anxiety disorder.

Religiosity

Participants will be asked to self-report their religious affiliation as Christian, Jewish, Muslim, Hindu, Buddhist, Sikh, Traditional (aboriginal) spirituality or No religion.⁴⁷ Religiosity will be measured by the Duke University Religion Index (DUREL) as a widely used, validated tool for assessing religious involvement.^{82 83} The DUREL is a 5-item, self-reported questionnaire with subscales to measure organisational religious association, non-organisational religious association and intrinsic religiosity. Items measuring organisational and non-organisational religious association are assessed on a 6-point scale from 1 to 6 with higher scores reflecting more frequent religious attendance. Items measuring intrinsic religiosity are assessed on a 5-point scale from 1 (*Definitely not true*) to 5 (*Definitely true of me*). Individual subscales scores will be summed and analysed separately.

Sample size calculation

Most previous studies investigating weight change in undergraduate students have used sample sizes between 75 and 200 participants.¹¹ With a sample size of 2000, there is at least 80% power to detect effect sizes of 0.8 kg/m² across a range of allele frequencies at the 5% significance level for BMI level (table 2). For reference, the risk allele of *FTO* increases BMI level by approximately 0.4 kg/m² and has a minor allele frequency of 0.4 in Europeans, although these differ by ethnicity.⁸⁴ For BMI change, there is at least 80% power to detect effect sizes of 0.1 kg/m²

Table 2 Sample sizes needed in a cohort design to detect significant associations of genetic variants with BMI level with 80% power and a two-sided P of 0.05 by beta coefficient and allele frequency for risk allele

Allelic beta	Minor allele frequency					
	0.01	0.05	0.1	0.2	0.3	0.4
0.10	513 741	107 071	56 508	31 784	24 215	21 188
0.20	128 432	26 765	14 112	7 943	6 051	5 294
0.30	57 079	11 893	6 275	3 528	2 687	2 351
0.40	32 105	6 688	3 528	1 983	1 510	1 321
0.50	20 546	4 279	2 257	1 268	965	844
0.60	14 267	2 970	1 566	879	669	585
0.70	10 481	2 181	1 149	645	490	429
0.80	8 023	1 669	879	493	374	327
0.90	6 339	1 316	694	389	295	258
1.00	5 134	1 067	561	314	238	208
1.50	2 279	472	257	137	104	90
2.00	1 280	264	137	75	57	49
2.50	818	167	86	47	35	30
3.00	567	115	59	31	23	19
3.50	415	83	42	22	16	13

BMI, body mass index.

Table 3 Sample sizes needed in a cohort design to detect significant associations of genetic variants with BMI change with a power of 80% and a two-sided P of 0.05 by beta coefficient and allele frequency for risk allele

Allelic beta	Minor allele frequency					
	0.01	0.05	0.1	0.2	0.3	0.4
0.01	>1 000 000	669 216	353 196	198 671	151 367	132 446
0.02	802 722	167 301	88 296	49 665	37 839	33 109
0.03	356 763	74 354	39 240	22 071	16 815	14 713
0.04	200 678	41 822	22 071	12 413	9 457	8 274
0.05	128 432	26 765	14 124	7 943	6 051	5 294
0.06	89 188	18 586	9 807	5 515	4 201	3 675
0.07	65 525	13 654	7 204	4 051	3 085	2 699
0.08	50 166	10 453	5 515	3 100	2 361	2 066
0.09	39 637	8 258	4 357	2 449	1 865	1 631
0.10	32 105	6 688	3 528	1 983	1 510	1 321
0.20	8 023	1 669	879	493	374	327
0.30	3 564	740	389	217	164	143
0.40	2 003	414	217	120	91	79
0.50	1 280	264	137	75	57	49
0.60	888	182	94	51	38	33
0.70	651	133	68	36	27	23
0.80	498	101	51	27	19	16
0.90	392	79	40	20	14	12
1.00	317	63	31	16	11	9

BMI, body mass index.

across a range of allele frequencies at the 5% level of significance (table 3). To account for a 20% dropout rate, an additional 500 individuals will be recruited for a final sample size of 2500.¹³ Dropout is defined as missing two consecutive appointments since it reflects one full academic year. Sample size estimates for GWAS, exome-wide association study for rare variants and associations for binary environmental traits are included for reference for BMI level (see online supplementary tables 1–3) and BMI change (see online supplementary tables 4–6). Our targeted sample size will provide reasonable to good statistical power for these analyses.

Statistical methods

Descriptive statistics at baseline will illustrate the distribution of sex, age, sexual orientation, civil status, socio-economic status, ethnicity, proportion born in Canada, distribution of economic status of birth country (high/middle/low income), residence status on/off campus, meal plan type (yes/no, high/medium/low cost), total and carbohydrate/fat/protein energy intake, alcohol consumption, physical activity, exercise motivation, electronic screen time, sleep quality, hair cortisol concentrations, history of sexual assault, impulsive personality traits, impulsive choice, disordered eating, body dissatisfaction, self-esteem, depressive symptoms, anxiety, religiosity, religious affiliation, BMI, WC, WHR, BFM and %BF. Continuous variables will be reported by mean and SD. Categorical variables will be reported by count and percentage. Subgroup analyses (eg, ethnicity) on obesity outcomes will be performed if there is a significant interaction between the predictor and the subgroup factor.

Analysis of environmental risk factors

The effect of potential environmental risk factors on obesity traits (ie, BMI, WC, WHR, %BF and BFM) at baseline will be tested using linear regression models with adjustments for age, sex and ethnicity. For variables such as sleep health which are evaluated by scaled questionnaires, the cumulative global score will be used in the analyses to increase power. The effect of each potential environmental risk factor at baseline and during follow-up on the evolution of obesity traits at 1 year (interim) and 3.5-year (final) post baseline visit will be tested using mixed effects linear regression models with adjustment for age, sex, ethnicity and baseline BMI. Multivariate hierarchical stepwise mixed regression models will be used to assess the independent effect of each environmental risk factor on obesity trait trajectories. Collinearity and sensitivity analyses will be conducted to ensure stability of the model. Mediation and interaction analyses will be conducted when there is scientific rationale or biological plausibility for a relationship between variables.

Analysis of genetic risk factors

All analyses will investigate associations with genetic variants at baseline, 1 year and 3.5 years post baseline. Heritability estimates for obesity trait level and change

will be calculated. GWAS will be performed to identify genetic variants associated with obesity trait level and change. Significance of genetic variants will be tested at the genome-wide level of significance ($P < 5 \times 10^{-8}$). Gene-based association tests for SNPs will also be performed for obesity traits. WES analysis will be performed to identify rare genetic coding variants associated with obesity trait level and change. Significance of SNPs and exonic variants will be tested at the gene-based level of significance ($P < 2.5 \times 10^{-6}$).⁸⁵ Hypothesis-free whole-genome approaches (GWAS and WES) do not have the power to detect all the genetic variants contributing to obesity because of the multiple testing burden from the Bonferroni correction.^{86–87} Testing a subset of strong candidate genes or SNPs reduces the number of tests conducted and has the potential to lead to the identification of obesity genes missed by conventional approaches.⁸⁸ These strategies will be conducted in GENEiUS. Genome-wide Complex Trait Analysis will be used to assess the heritability of obesity traits and change in obesity traits from SNP variants previously identified by GWAS.⁸⁹ The PLINK software will be used for GWAS.⁹⁰ Autosomal and X chromosome SNPs will be imputed using the all ancestry 1000 Genomes Project reference panel and the miniMAC or IMPUTE2 software.^{91–92} Gene-based association of SNPs with obesity trait level and change will be assessed using VEGAS2 software.⁹³ Variant annotation and filtering from whole-exome sequences will be performed using the KGGSEQ framework.⁹⁴

The association of well-established GWAS SNPs for BMI, WC, WHR and %BF, or a combination of pathogenic mutations in previously identified monogenic genes, with obesity trait level and change at baseline will be performed using linear regression models with adjustment of age, sex and ethnicity/population structure.^{53–55} The self-reported ethnicity will be verified using principal component analysis from the EIGENSTRAT software.⁹⁵ Adjustment for ethnicity/population structure will be achieved by adding the 10 first principal components of EIGENSTRAT analysis in the regression model. A P value threshold of 0.05 will be considered significant given the high prior likelihood of association. SNP variants will be analysed individually and cumulatively as a gene score using additive, dominant and recessive modes of inheritance. An unweighted gene score, which estimates the effect of all obesity susceptibility genetic variants on obesity traits, will be calculated by summing the alleles positively correlated with individual obesity traits.⁹⁶ Missing genotype values will be imputed using the method of the mean in the calculation of the gene score. This imputation will be performed for each SNP individually using the arithmetic average of the coded genotypes observed for all the successfully genotyped individuals in each ethnic group. An allelic burden test of functional mutations for previously identified obesity genes will be conducted to investigate the cumulative effect obesity genes mutations on obesity trait level and change. All models will be adjusted for age, sex and ethnicity/population structure. Interim

and final analyses will also be conducted to determine the effect of predisposing obesity genetic variants on individual obesity traits and changes in obesity traits with adjustment for age, sex, ethnicity and baseline BMI.

Prediction models of weight change

Models will be created to assess the utility of genetic variants and environmental factors on predicting weight status. Support vector machine learning models will be used to determine the optimal combination of predictive SNPs for incident occurrence of overweight and/or obesity.⁹⁷ Receiver operating characteristic curve and net reclassification improvement analyses will include environmental and genetic factors to estimate their ability to predict overweight, overweight/obese or obese status in undergraduate students.^{98–99} Optimal predictive values for continuous environmental traits will be determined by polychotomisation as previously described.¹⁰⁰ Internal validation of the prediction models will involve training-testing split methods.¹⁰¹

DISCUSSION

Weight changes occurring in young adulthood may be important for the development of chronic obesity.⁶ However, this age group has been poorly studied. The GENEiUS study is the first adequately powered observational study design aiming to investigate genetic and environmental associations of weight change in undergraduate students. The majority of past studies investigating undergraduate weight gain have only followed students until the end of their first academic year (ie, 6–8 months); therefore, little is known about weight changes throughout undergraduate studies.¹¹ The GENEiUS study aims to fill this knowledge gap by following students prospectively over their first 4 years of undergraduate study. The longitudinal nature of GENEiUS will permit the study of temporal relationships between obesity risk factors and strengthen the ability to make causal inferences regarding determinants of undergraduate weight change. This study includes the measurement of many well-established risk factors for obesity such as energy intake, physical exercise and sleep duration.¹⁰² GENEiUS will also investigate novel potential risk factors like exercise motivation, history of abuse, religiosity, stress measured by hair cortisol and the effect of immigration. Only few studies in undergraduate students have included the measurement of WHR, %BF or BFM.¹¹ Since BMI may be a biased estimate of body fat, the inclusion of these measures in GENEiUS will provide a better estimation of adiposity.¹⁰³ While it may be argued that measurement of additional cardiometabolic outcomes (eg, type II diabetes, hypertension, dyslipidemia, fatty liver, atherosclerosis) may be important, these comorbidities are mainly driven by obesity in young adults at the population level.^{104–106} For this reason, evolution of obesity-related traits will be our main focus. The heterogeneous nature of the sample population consisting of multiethnic students from a

variety of undergraduate programmes will also help to increase the generalisability of findings in North America and perhaps identify ethnic-specific effects.

While the GENEiUS study design has many strengths in its design, it also has limitations. First, it is restricted to measurement of only two time points each year from September to October and from March to April, without inclusion of a summer assessment. Since few students remain on campus during this period, a summer time point will be avoided. Further, while the great use of validated questionnaires will provide strong estimates for various environmental factors, many of these do not represent the criterion measure for their respective traits. For instance, the GPAQ overestimates moderate-to-vigorous physical activity when compared with accelerometer data.¹⁰⁷ These short, validated questionnaires delivered online were selected by balancing accuracy and feasibility given the large sample size of the study. Although dual-energy X-ray absorptiometry is a more precise measure of adiposity, BIA will be used in the present study to increase access to the equipment, decrease participant burden and limit cost.¹⁰⁸ BIA is limited by its sensitivity to fluid changes, the position in which participants stand and equations for %BF and BFM may not be generalisable to all ethnicities.¹⁰⁹ Further, this study is only conducted at one institution and thus results may not be generalisable to other universities. The single-centre design, however, results in less variability of certain environmental factors including type of cafeteria food, food accessibility and access to physical fitness facilities to be held constant. Finally, the GENEiUS study is not sufficiently powered to find gene–environment interactions which require samples of up to 100 000.¹¹⁰ Certain subgroup analyses with a low number of individuals, such as Aboriginal Peoples in ethnic-specific analyses, may also be underpowered to find associations.¹¹¹

Overall, the GENEiUS study is the first to investigate the genetic and environmental determinants of weight change in undergraduate students. It will assess a wide range of well-studied and novel potential risk factors. It will contribute to the limited knowledge of weight change throughout undergraduate studies as it will follow participants longitudinally. The prospective nature of this observational study will help to make causal inferences for weight change in undergraduate students. Since the duration of obesity is associated with higher morbidity and mortality, understanding the determinants of weight gain in young adulthood may lead to major improvements in the quality of life and life expectancy, as well as decrease the burden that obesity places on public health infrastructure.

Ethics and dissemination

Prior to enrolment, a member of the research team will explain the consent form in plain language and each student then will be asked to read and provide written informed consent. The informed consent states the voluntary nature of participation and that

withdrawal from the study may be done at any time. All methods and procedures for this study (#0524) were reviewed and approved by the Hamilton Integrated Research Ethics Board. Outcomes for this research will be published in peer-reviewed journals and presented at scholarly regional, national and international meetings. Meetings will occur with university leaders like the associate dean of education, administration and student groups at McMaster University to facilitate knowledge translation to the local stakeholders and student population.

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Contributors All authors designed the study protocol; REM and DM wrote the manuscript; CL, AA, AFI, FTY, AJM, HR, JM and MP critically reviewed the manuscript for important intellectual content; DM had primary responsibility for final content. All authors read and approved the final manuscript.

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