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Research Article

The link between allergic disease and depression in young adults: A structural equation modelling analysis

Abstract

Background: The co-occurrence of multiple interacting medical and psychological disorders is extremely common. A significant association between allergic disease (ADz - e.g., asthma, allergic rhinitis, allergic dermatitis) and depression has been reported.

Objective: Path analysis models using cross-sectional data were constructed to evaluate the inter-relationships among underlying co-occurring factors known to impact depression in young adults.

Method: 885 college students (21.80 ± 3.22 years old) completed an online survey assessing current ADz, sleep quality, pain/discomfort, Body Mass Index, stress, substance use, Internet addiction, physical activity, social support and depression.

Results: Our findings suggest that ADz is only one of multiple factors modulating depression. Six factors had significant direct effects (all $p < .05$) on depression: female gender, sleep quality, pain/discomfort, stress, Internet addiction, and social support. ADz, Body Mass Index, and substance use had only indirect effects (all $p < .05$). Social support was associated with better sleep, less depression and less stress. Physical activity had no measurable effect on depression.

Conclusions: This study is the first attempt to evaluate the complex interrelations between ADz, depression and co-occurring factors. The complex interactions between variables in the model highlight the need to study these factors conjointly. Future longitudinal studies are needed to determine the temporal order and to validate causal pathways.

Abbreviations

ADz – Allergic Disease (i.e., asthma, allergic rhinitis, allergic dermatitis); AR – Allergic Rhinitis; AUDIT – Alcohol Use Disorders Identification Test Total Score; BMI – Body Mass Index; FTND – Fagerström Test for Nicotine Dependence; IPAQ – International Physical Activity Questionnaire; PA – Physical Activity; MET – Metabolic Equivalent of Task; PSQI – Pittsburgh Sleep Quality Index; SSSQ-6– the 6-item Social Support Questionnaire, Satisfaction score; CESD – Center for Epidemiologic Studies Depression Scale; YIAT – Young's Internet Addiction Test.

Introduction

Depression is one of the most common mental health conditions [1]. It is characterized by a loss of positive affect with persistent symptoms including lack of self-care, poor concentration, anxiety, lack of energy, and loss of interest [2]. In 2011, 20.1% of U.S. adults reported depressive symptoms [3], with women more likely than men to suffer it (1.5 – 3 times)

[1,4–6]. In 2016, adults aged 18–25 had the highest prevalence of major depressive episodes (10.9%) [1]. The economic burden of depression exceeds $210 billion per year, with less than half (45-47%) attributable to direct costs [7]. But, this cost can be seriously underestimated if the long-term personal burden of depression, such as reduced educational attainment, lower earning potential, increased chance of teenage childbearing, higher unemployment, and increased work disability are not taken into account [8]. Such long term personal burden has a more damaging impact on the young [9,10], (18–34 years) who experience the highest incidence (24%) [11] and highest cumulative prevalence of depression [12]. Further, the high incidence of depression combined with its current high relapse rate place emerging adults at particularly high-risk, with poorer psychosocial functioning, more severe chronic episodes, comorbid anxiety, and suicidality than any other age group [11]. Furthermore, although most patients with depression will not commit suicide, one third will make an attempt sometime during adolescence or young adulthood, and, 2.5% – 7% will commit suicide by young adulthood [13]. Depression increases

the risk for suicide by more than 15-fold [14]; further, increased depression severity increases risk for suicidality [15]. Suicide is a leading cause of death in the US; suicide rates increased by more than 30% from 1999 through 2016 [16]. Of great concern is the increase in suicide rate among young people (< 34 years of age) [17,18]. In 2013, suicide was the second leading cause of death for people ages 15-24 years, the second for ages 25-34 years, the fourth for ages 35-54 years, the eighth for those aged 55-64 years, and the seventeenth for those ≥ 65 years [18]. It is speculated that the upsurge in depression rates over the past 10 -15 years [19-21], is the result of major societal and economic changes creating significant stressors for emerging adults [22], such as lack of structure, poor time and disease management, instability of personal relationships, struggle for economic independence, and uncertainty about the future and one's competence to handle it [23-25]. According to the Cooperative Institutional Research Program Freshman Survey, college students' self-rated emotional health has been declining [26]. In 2017, 40.2% reported feeling so depressed "that it was difficult to function," two-thirds (62%) reported experiencing "overwhelming anxiety," nearly half (44.8%) reported more than average stress, and 11.6% reported tremendous stress [27]. Electronic media and the Internet in particular, have exacerbated stressors for young people. Internet usage in young adults and college graduates is pervasive [28]. Some researchers blame Internet use for the rise in depression [29-32] and suicide[33,34], arguing that spending too much time using electronic devices prevents young people from engaging in face-to-face social activities that might help protect against depression [35-37]. The increase in Internet use has been linked to clinical symptoms of dependence that interfere with a person's daily life, similar to gambling and drug dependence, leading to the recognition of *Internet addiction* as a psychiatric disorder associated with depression [38]. The link between Internet addiction and depression may be mediated by sleep disturbance or insomnia [30,39]. These findings are pertinent here because college students experience insufficient and poor-quality sleep, as well as growing levels dissatisfaction with their sleep [40-42]. Poor-quality sleep among young adults may be reaching epidemic proportions, with 73% of college students reporting sleep problems that include insufficient sleep, difficulty falling asleep, sleep disturbances, and excessive daytime sleepiness [43,44]. Insomnia and sleep disturbances are considered to be core symptoms of depression;[2] however, recent studies suggest a different causal pathway [45-47]. Specifically, the evidence shows a detrimental effect of poor sleep on emotional functioning (i.e., daytime mood, emotional reactivity and regulation)[48], suggesting that sleep difficulties precede and trigger the symptoms of depression [45-47,49,50]. Depression is also associated with psychiatric and medical comorbidity, chronic pain, insomnia [49,51,52], impaired functioning, and suicidality [53,54]. For example, patients with persistent pain experiencing sleep problems at baseline had more than three times the risk of developing depression [51]. Untreated conditions such as allergy, pain, and insomnia have a tremendous impact on a person's quality of life. Yet, there is evidence that emerging adults, particularly young men, access health services less often than any other age group: 59% of young adults report having a usual source of care, and those without a regular source of care had significantly lower utilization of outpatient services (except emergency room – ER visits), than those who have a regular source of care [55]. Young adults also have lower rates of health care utilization (83% vs.72%), lower rates of office visits (67% vs. 55%), and a higher rate of ER visits than adolescents (12% vs. 15%) [55]. Further, poor-health practices and risky behaviors such as substance use increase during emerging adulthood [15,56], and have been clearly identified as major risk factors for depression [57-59] and suicidality [60].

Most theoretical accounts of depression propose a diathesis-stress model in which stressors may activate a diathesis or vulnerability, triggering a depressive event [61-65]. According to this view, there is a synergistic relation between the diathesis and stress which results in depressive symptomatology being greater than would be expected by their independent effects; that is, the effects are multiplicative. According to these models, vulnerabilities -- temperament, physiological, cognitive or genetic characteristics -- may negatively potentiate the effect of environmental stressors [64,65]. However, progress in understanding and treating depression as accounted by these models has been slow and challenged by methodological concerns [66]. Rather than vulnerabilities (e.g., temperament, attributional style, and specific genes), some argue, individual characteristics may function as *plasticity factors*, impacting how susceptible individuals might be to environmental influences [66]. Recently, a network perspective was proposed as a theoretical alternative to understand depression [67-69]. A network perspective assumes that depression is the result of direct interrelations among sets of symptoms. For example, symptoms (such as wheezing, runny nose, post-nasal drip) trigger other symptoms (like trouble with sleep, fatigue, and poor concentration) which, over time, lead to depressive symptoms and suicidal behaviors that further exacerbate stress, pain/ discomfort, and sleep. At the heart of the theory is the notion that symptoms of co-morbid conditions are causally connected through multiple mechanisms [69]. The presence of multiple interacting medical and psychological disorders is extremely common, and the link between mood disorders, particularly depression, and allergic disease (ADz - e.g., asthma, allergic rhinitis, and atopic dermatitis) is widely accepted [70-76]; however, the mechanisms underlying such associations are still not understood.

ADz is a major cause of disability, health resource utilization, and poor quality of life for those who are affected [77]. Asthma is the most common chronic disease among children and young adults [77]. In 2011, 15.6% of Americans 15-34 years reported lifetime asthma [78]. The condition may worsen due to allergic rhinitis (AR), a common comorbid, underdiagnosed, and often undertreated condition [79,80]. Approximately 80% of all patients with asthma have co-morbid AR [81]. Compared to those with asthma alone, patients with asthma and comorbid AR tend to have more asthma exacerbations, more visits to their primary care provider, more ER visits, and more hospitalizations [81]. It has also been shown that AR significantly impacts all dimensions of sleep [81-84]; indeed, patients are considered to have moderate/severe AR if they experience sleep disturbance and/or impairment of daily

activities [81-85]. An association between ADz and insomnia has also been reported. For example, Meltzer [86], found that adolescents with severe asthma get insufficient sleep, have poor sleep hygiene, and experience clinically significant insomnia. The data revealed a dose response pattern where adolescents with severe asthma were more likely to report insomnia than all other comparison groups: adolescents with no asthma, lifetime-asthma, mild, or moderate asthma [86]. In addition, compared to patients without asthma and/or AR, patients with asthma [87-90] and patients with AR are more likely to report symptoms of depression [70,72,74,81-85,91-95].

In recent years, numerous cross-sectional studies have shown a link between obesity and asthma [96-99]. Obesity is one of the most ubiquitous conditions worldwide [100]. In 2017, 33.6% of college students in the US were overweight or obese [27]. Further, obesity has been associated with reduced quality of life and multiple other comorbidities including insomnia / sleep disturbances [97,101,102,103], pain / discomfort [97,104] and depression [97,101,105,106], but not atopy [97,99]. Depression rates among obese individuals are 1.5-2 times higher than normo-weight individuals [105,107,108]; this increased rate is more evident among females [105]. There is evidence suggesting that depression may be an underlying mechanism linking increased Body Mass Index (BMI ≥ 25) and poor asthma control [98,109,110]. Given its high prevalence and impact on quality of life, identifying factors that may prevent or reduce the impact of depression is paramount; evidence suggests that social support [36,37,111,112] and physical activity (PA) [113-115], are two promising protective factors in the prevention of future depression.

The evidence suggests that depression is a multifactorial disorder. However, we found no published studies looking at the inter-relationships among factors known to concurrently impact depression such as ADz, sleep quality, pain/discomfort, BMI, stress, substance use, Internet addiction, physical activity, social support, and depression among emerging adults. The purpose of this exploratory study was to investigate these relationships utilizing multivariate modeling that allows for the simultaneous statistical examination of multiple relationships [116]. To address the objective of this study, we constructed seven quantitative models and tested them using multivariate techniques (i.e., structural equation modeling - SEM), which afforded us the opportunity to examine both direct and indirect effects of variables influencing depression. We hypothesized that *1) ADz is significantly associated with depression only indirectly through its negative impact on sleep quality; 2) the impact of ADz on depression is also mediated by stress and pain / discomfort); 3) BMI is only indirectly associated with depression through its negative impact on sleep quality, increased pain / discomfort, and stress; 4) higher stress is directly and indirectly associated with higher depression through its direct negative impact on sleep quality and increased pain / discomfort; 5) substance use is directly and indirectly associated with depression through its negative impact on sleep quality, increased pain / discomfort, and stress; 6) Internet addiction is directly and indirectly associated with depression through its negative impact on sleep quality and stress; 7) higher levels of physical activity and social support are directly and indirectly associated with better sleep quality and less stress, pain / discomfort, and depression.*

Methods

Participants

A sample of 985 college students was recruited from a large university in the southwestern U.S. who completed the study to satisfy a class requirement. Participants were told the purpose of the survey was to study the lifestyle of college students. Thirty-nine non-traditional students ≥ 34 years of age were excluded, 46 records were excluded due to missing data to evaluate sleep, and 14 records were excluded for other missing data, yielding a total sample of 885 complete records. The sample's average age was 21.80 (SD=3.22) years, mostly females (79.4%). The study was approved by the University Committee on Human Subjects. No personal identifiers were collected and, after reading a description of the study, participants gave passive consent by proceeding to complete an online survey.

Measures

Depression was measured by the Center for Epidemiologic Studies Depression Scale (CESD) [117]. To prevent overlap and the potential inflation of correlations, item 11 (My sleep was restless) was removed; thus scores in the $CESD_{19}$ ranged from 0 to 52. The CESD has good test-retest reliability and has been validated in various populations, including adolescents [118], (Cronbach's α for the $CESD_{19}$ was .917). A CESD score ≥ 16 identifies individuals with clinically relevant symptoms [117].

Allergic disease was ascertained by several questions: first, students were asked "have you ever received a physician's diagnosis of asthma (No or Yes); students who answered *yes* were asked if they "have been taking any prescribed medications or treatment for asthma" (No or Yes). Those who answered both questions positively were classified as having *current asthma* (0-No or 1-Yes). Then, they were asked if they had been diagnosed with food allergies or allergies to airborne allergens such as dust mites, pet dander, mold, or pollen. *Current allergy* identification was based on doctor-diagnosis of other allergies (i.e., dust mites, pet dander, mold, pollen, etc.) and a positive answer to either "Have you been prescribed medications to treat your allergy (ies)?" or "In the past month, did you take any over-the-counter allergy medication (such as Allegra, Benadryl, Claritin, Clarinex, Sudafed, and Zyrtec)?" (0-No or 1-Yes). A binary variable *ADz* (0-No or 1-Yes) was created by combining having current asthma and/or having current allergy.

Sleep was measured with the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a standardized, questionnaire composed of 19 questions grouped into seven components (1: Subjective sleep quality, 2. Sleep latency, 3. Sleep duration, 4. Sleep efficiency, 5. Sleep disturbance, 6. Use of sleep medication, and 7. Daytime dysfunction) with high levels of consistency, reliability, and validity (Cronbach's α for this study of .683) [119]. The PSQI was scored following the authors' proposed algorithm [119] and the global score (0 – 21) was treated as a continuous variable (higher scores indicating worsening problems). A cut-off score > 5 has been recommended for clinical use as indicative of poor quality sleep [119].

Pain / discomfort was assessed by a question from the Canadian Community Health Survey, "Are you usually free of pain or discomfort?" [120] (0-No or 1-Yes). Those who answered "No" were classified as experiencing pain / discomfort.

Obesity was measured as BMI calculated using self-reported height (in) and weight (lb) with the formula: [weight /height²]x 703.

Stress was measured by the Inventory of College Students Recent Life Experiences [121]. The inventory is a self-report questionnaire consisting of 49 *daily hassles* rated on a four-point Likert scale to estimate level of stress caused by daily life experiences over the past month. This inventory has shown high levels of consistency, validity, and reliability (Cronbach's α for this study of .94). Total score is calculated by adding all items (range 49 – 196); lower scores indicate low level of stress; no clinical cutoff score has been established. Most studies with college students report a mean score of around 95, with higher scores for women than men [121-124].

Alcohol use. Binge or heavy episodic drinking was assessed using a single item from the Youth Risk Behavior Surveillance System [125]. Problem drinking was identified with the Alcohol Use Disorders Identification Test total score (AUDIT; range 0–40) [126], a 10-item self-administered measure designed to identify problematic drinking behavior in the last 30-days (Cronbach's α for this study of .84). A cutoff score of ≥6 successfully identified 91% of the high-risk college drinkers [127]; compared to the traditional cutoff score of ≥8 that identified only 82%.

Smoking and nicotine dependence were assessed with the Fagerström Test for Nicotine Dependence (FTND). The FTND is highly reliable, with scores ranging from 0 to 10; the higher the score, the more intense the physical dependence on nicotine (Cronbach's α for this study of .70) [128-129].

Internet addiction was measured using Young's Internet Addiction Test (YIAT) [14]. The YIAT consists of 12 questions to assess the effects of daily Internet use using a 5-point Likert scale (Cronbach's α for this study of .90) [14]. A total score, ranging from 12 to 60 is calculated by adding all items. A score > 30 is suggested as indicative of problematic use, and one > 37 as indicative of pathological use [14].

The International Physical Activity Questionnaire – short form (IPAQ) was used to assess physical activity (PA); it is a 9-item instrument consisting of six items reporting the number of days (frequency) and the number of minutes per day (duration) participants engage in PA during the last seven days. Due to a glitch, data on walking and sitting were lost. Thus, the PA score was calculated for vigorous and moderate activity as Metabolic Equivalent of Task (MET) minutes per week applying guidelines of the IPAQ research committee to the available data [130]. According to the scoring method, *vigorous* PA is equal to weekly PA expenditure multiplied by 8 METs, and *moderate* PA equals weekly expenditure multiplied by 4. A total MET weekly score was calculated by adding the METs for moderate and vigorous PA. This score has been used to classify individuals according to volume of activity as low (< 600 MET/min), moderate (600–1,499 MET/min), and high (≥ 1,500 MET/min) [131,132].

Satisfaction with social support was measured with the 6-item Social Support Questionnaire [133]. Participants were asked to indicate the number of supporters, and to rate their level of satisfaction with the support provided using a 6-point Likert scale. The Satisfaction Score (SSSQ-6) was calculated by adding all ratings (range 6 - 36). Scores ≤ 33 are considered indicative of low satisfaction with available social support [35,134,135].

Procedure

All statistical analyses were performed using SPSS 24 and AMOS 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp). Both univariate and multivariate normality was assessed for all observed variables (skewness and kurtosis), followed by proper transformations into Z-score. A series of binary variables were created by dichotomizing into groups students with and without (0 = No and 1 = Yes) ADz, and pain / discomfort. We examined the relationships between the predictors (i.e., ADz, BMI, alcohol and tobacco use, PA, and SSSQ-6) and the outcomes (i.e., sleep quality, pain / discomfort, stress, and depression) using χ^2 test for categorical measures and t-test for independent samples for continuous measures. Path-analytic techniques were used to test whether the effect of the predictors on depression was direct or indirect.

Mediation models

Based on evidence from the literature, seven mediation path models were constructed using AMOS 24.0 [136,137] (Figure 1). Model 1: The primary outcome was depression as CESD₁₉ score, a continuous variable; having current ADz was the main predictor variable. Then, variables associated with depression were sequentially added in each model: Model 2 - Pain / discomfort (mediator), Model 3 – BMI (predictor), Model 4 - Stress (mediator), Model 5 – alcohol and tobacco use (predictors), Model 6 – Internet addiction (predictor), and Model 7 – PA and SSSQ-6 (predictors). The participant's gender was entered as a control variable, as it has been reported to have a moderating effect on depression [4-6], stress and sleep [138-139] and the relationship between sleep and BMI [138-141]. Mediation analysis assumes both causal and temporal
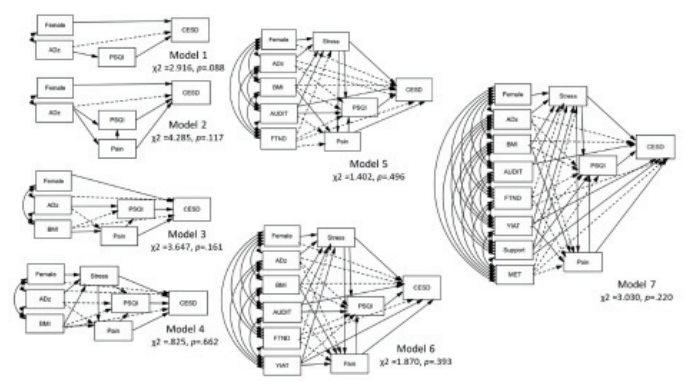

Figure 1:

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relations and it has been used to attain a deep understanding of disease pathology and the mechanisms through which variables influence the condition [142]. When performed using strong evidence, prior theory, and with appropriate context, mediation analysis may provide the basis for future intervention research [142]. Bootstrapping was used to assess the direct, indirect, and total effects of the predictors on outcomes [143]. The models goodness of fit was ascertained using χ^2 ($p > .05$, suggesting the absence of meaningful unexplained variance); however, χ^2 is sensitive to sample size, thus we also used the ratio of χ^2 to df (χ^2 / df – where a ratio smaller than 3 is considered indicative of an acceptable data model fit). Furthermore, the Comparative Fit Index (CFI) and Standardized Root Mean Square Residuals (SRMR) were also used as evidence of model fit. Values greater than .95 for CFI, and lower than .08 for SRMR are considered evidence of a well-fitted model [144].

Results

Descriptive statistics for the variables in this study are shown in table 1. The sample was comparable to the student population in the psychology program, being mostly females (79.4% vs. 75.3% respectively), and Caucasian (58.1% vs. 55.9% respectively). One-hundred eleven (12.5%) students reported having current asthma, and 121 (13.7%) current allergy. Forty percent of those with "current asthma" also reported "current allergy" ($\phi = .336$; $p < .001$). About one fifth of the students (20.7%) had either current asthma or allergy, and 5.5% had both. One fifth (20.7%) of the students also reported pain / discomfort. Of the students who reported pain / discomfort (n=183), 27.3% had current ADz. Compared to students without ADz, significantly more students with ADz reported pain /

discomfort (18.9% vs. 27.3%, $p = .013$) and had higher PSQI scores (7.22 vs. 8.00, $p = .002$) which is indicative of poorer sleep quality. About one third of the students (35.3%) were either overweight or obese (BMI ≥ 25); and 13.6% were obese (BMI ≥ 30). The overall mean CESD score (20-item scale) was 16.13 (SD = 10.84), with 43.7% of the students showing some level of depression (CESD ≥ 16), and 18.9% scoring ≥ 26, suggesting severe depression. The average IDH stress score was 95.75 (22.98), similar to levels reported in other college populations, with higher scores for women than men (97.31 vs. 89.72) [121-124]. The top quartile of the IDH scores ranged from 109 – 184. As shown in table 1, students with depressive symptomatology (i.e., CESD ≥ 16) reported significantly worst sleep quality (i.e., PSQI), more pain and stress, heavy drinking (i.e., AUDIT), tobacco addiction (i.e., FTND) and Internet addiction (all $p < .05$). They were also more likely to be female, have reported lower levels of PA (i.e., MET min / week) and being less satisfied with their social support (all $p < .05$). Similarly, compared to their peers without the conditions, students with current ADz, and those who experienced pain and discomfort had significantly poorer sleep quality, higher level of depression (CESD$_{19}$), and stress (all $p < .05$). In addition, students who experienced pain and discomfort were significantly older, with higher BMI, and reported significantly less satisfaction with their social support ($p < .05$).

The PSQI mean score was 7.38 (SD = 3.34), 68.8% experienced poor sleep quality (score > 5). Most students reported restricted sleep; only 26.0% reported eight or more hours of sleep. Perhaps resulting from poor sleep, 24.0% of the students reported daytime dysfunction (score ≥ 2, range-0-3).

Table 1: Sample characteristics and comparison between students with depression (CESD ≥16) and those without (CESD < 16) for study variables (i.e., Age, Female Gender, ADz, PSQI, Pain / Discomfort, STRESS, AUDIT, current smokers, FTND, MET min / week, and Satisfaction with Social Support. Values for t - test are shown as means and standard deviations (SD), and values for χ2 as frequencies and percentages (%).

Variables	N=885	CESD ≥ 16 n=387	CESD < 16 n=498	p	ADz Yes n=183	ADz No =702	p	Pain Yes n=183	Pain No n =702	p
Age	21.80 (3.21)	21.63 (3.52)	21.94 (3.52)	.138	21.86 (3.29)	21.79 (3.20)	.801	22.51 (3.58)	21.62 (3.093)	.002
Females	703 (79.4%)	159 (84.5%)	376 (75.5%)	.001	159 (86.9%)	544 (77.4%)	.005	143 (78.1%)	560 (79.8%)	.627
ADz	183 (20.7%)	91 (23.5%)	92 (18.5%)	.079						
CESD$_{19}$					16.39 (1.76)	14.63 (1.25)	.040	2.08 (11.11)	13.67 (9.76)	<.001
BMI	24.46 (5.23)	24.56 (5.60)	24.34 (5.13)	.614	24.94 (5.60)	24.34 (5.13)	.187	25.82 (6.46)	24.10 (4.80)	.001
PSQI	7.38 (3.35)	8.81 (3.33)	6.27 (2.89)	<.001	8.00 (3.74)	7.22 (3.21)	.010	8.98 (3.67)	6.96 (3.11)	<.001
Pain	183 (2.7%)	119 (30.7%)	64 (12.9%)	<.001	50 (27.3%)	133 (18.9%)	.013	-	-	-
STRESS	95.75 (22.97)	109.85 (21.40)	84.79 (17.55)	<.001	100.37 (23.92)	94.54 (22.59)	.002	102.76 (24.17)	93.92 (22.31)	<.001
AUDIT	4.07 (4.50)	4.05 (4.59)	3.75 (4.22)	.017	4.16 (4.14)	4.05 (4.59)	.768	3.84 (4.21)	4.13 (4.57)	.439
Current smokers	48 (5.4%)	27 (7.0%)	21 (4.2%)	.075	10 (5.5%)	38 (5.4%)	.889	15 (8.2%)	33 (4.7%)	.068
FTND	.242 (1.04)	.32 (1.21)	.18 (.88)	.049	.25 (1.07)	.24 (1.03)	.891	.36 (1.23)	.21 (.98)	.129
YIAT	24.65 (8.23)	26.84 (9.01)	22.95 (7.13)	<.001	25.55 (8.55)	24.42 (8.14)	.098	25.82 (6.46)	24.08 (7.94)	.295
MET min / week	973.06 (963.39)	870.08 (919.14)	1053.09 (989.96)	.005	1069.07 (987.68)	948.03 (956.09)	.130	863.82 (94.88)	1001.54 (967.86)	.085
SSSQ-6	33.40 (4.11)	32.26 (4.72)	34.28 (3.32)	<.001	33.14 (4.27)	33.47 (4.07)	.335	32.79 (4.62)	33.56 (3.96)	.040

ADz – current allergy or asthma; AUDIT - Alcohol Use Disorders Identification Test; BMI – Body Mass Index; CESD – Center for Epidemiological Studies Depression; FTND - Fagerström Test for Nicotine Dependence; YIAT – Internet Addiction Test; Pain – Pain / Discomfort; PSQI – Pittsburg Sleep Quality Index; MET - Metabolic Equivalent of Task; SSSQ-6 – Satisfaction with Social Support.

One-fifth (20.0%) reported taking sleep medication once a month (PSQI – Component 6), and 9.4% taking sleep medication once a week. Most participants reported sleep disturbances (97.3%); 19.8% reported loud snoring, and 8.0% reported experiencing long pauses between breaths at least once a month, both symptoms suggestive of sleep apnea. Further, students with ADz and those who experience pain and discomfort reported significantly more sleep disturbances (p < .001) than their counterparts who reported no ADz or pain / discomfort.

Reported ≥ 1 alcoholic drinks in the past month, 40.2% reported ≥ 1 episodes. Forty-eight students (5.4%) reported current smoking, only two reported smoking ≥ 10 cigarettes daily, most were classified as light smokers (n=46, 95.8%), and only 3.4% had nicotine dependence (FTND ≥ 5). Almost all student (91.2%) had an account in a social networking site. The mean YIAT was 24.65 (SD = 8.23); with 20.1% of the students scoring > 30 (indicative of problematic use), and 6.1% scoring > 37, suggestive of pathological use [145].

Almost half (45.3%) of the students reported IPAQ < 600 MET min/week; 29.2% between 600-1500 MET min/week 258; and 25.5% reported >1500 MET min/week. There were no significant differences in PA between students with ADz and those without the diagnoses, and between those in pain and those with no pain / discomfort (Table 1). There were, however, significant differences in PA between males and females. As reported by others [146-148], females in our sample were significantly less active than males (906.23 vs. 1231.21 MET min/week, p < .001). Females also reported significantly more ADz (p = .005), more depression (p < .001), lower sleep quality (p = .05), and more stress (p < .001). On the other hand, women had lower rates of alcohol use (p = .002) than males. Overall, students in our sample reported low levels of SSSQ-6 (mean = 33.40, median = 35, range 0 – 36) [35,134,135]. SSSQ-6 was lower for males than females (32.65 vs. 33.59, p < .05). There

were no significant differences in pain / discomfort or smoking rates between males and females. Inspection of the correlation matrix shows bivariate correlations within acceptable range, that is r < .700 (Table 2) [144]. It is worth noting that depression ($CESD_{19}$) had significant positive correlations with *female gender* (r = .114, p<.01), *Stress* (r = .654, p <.001), *PSQI* (r = .443, p<.001), *Pain / discomfort* (r = .251, p <.001), *ADz* (r =.069, p< .05), *FTND* (r = .070, p < .05), and *Internet Addiction* (r = .283, p < .001), and negative correlations with *MET* (r = −.097, p <.01) and *SSSQ-6* (r = −.282, p <.001).

Mediation Analysis. Several alternative models were compared in terms of fit and efficacy in accounting for inter-relationships among ADz, sleep quality, pain/discomfort, BMI, stress, substance use, Internet addiction, SSSQ-6, PA, and depression in emerging adults. Gender was entered as a control variable in all models. As shown in table 3, all models (Figure 1) showed acceptable fit (all χ^2 p > .05, the ratio of χ^2 to df all < 3, CFI all > .95 and SRMR all < .08) [144]; the differences in fit indices were likely due to a greater parsimony (i.e., fewer parameters) of Models 1 – 6 relative to Model 7 (See Table 3). Model 7 fits the data well and includes the most important contributors to depression reported in the literature. Model 7 accounts for 25.6% of the variance in sleep quality, 6.0% of the variance in pain, 18.6% of the variance in stress, and 49.3% of the variance in depression (Table 3). This model sheds light on the interactions among multiple factors, and may be helpful in the planning of future research looking for opportunities to treat and prevent depression in young adults with ADz and co-morbid conditions.

Regression coefficients and a summary of direct, indirect, and total effects identified in Model 7 are reported in table 4. The three most important factors predicting depression were stress (total effect of β = .594, direct effect of β = .512, and indirect effects β = .082, all p < .001), SSSQ-6 (total effect of β = −.239, direct β = −.102, and indirect effects β = −.137, all p <

Table 2: Correlation matrix for study variables.

	$CESD_{19}$	PSQI	Pain	ADz	BMI	STRESS	AUDIT	FTND	YIAT	MET	SSSQ-6
Female	.114**	.066	-.016	.094**	-.104**	.134†	-.121†	-.022	-.025	-.136†	.092**
$CESD_{19}$		.443†	.251†	.069*	.027	.654†	.065	.070*	.283†	-.097**	-.282†
PSQI			.245†	.095**	.016	.444†	.109**	.069*	.117†	-.025	-.242†
Pain				.084*	.133†	.156†	-.026	.058	-.035	-.058	-.076*
ADz					.047	.103**	.010	.005	.056	.051	-.032
BMI						.070*	-.049	-.013	.012	-.033	.000
STRESS							.110**	.038	.327†	-.079*	-.235†
AUDIT								.159†	.042	.064	-.065
FTND									-.072*	-.087†	-.032
YIAT										-.083*	-.201†
MET											.088**

† p < .001 level
** p< .01 level
* p< .05 level

ADz − current allergy or asthma; AUDIT - Alcohol Use Disorders Identification Test; BMI − Body Mass Index; CESD − Center for Epidemiological Studies Depression; FTND - Fagerström Test for Nicotine Dependence; YIAT − Internet Addiction Test; Pain − Pain / Discomfort; PSQI − Pittsburg Sleep Quality Index; MET - Metabolic Equivalent of Task; SSSQ-6 − Satisfaction with Social Support.

Table 3: Fit indices for Models Tested in Structural Equation Model Analyses.

	Predictors				Variance Explained				Model fit				
	BMI	Substance use	YIAT	Protective	Stress	Pain	PSQI	CESD	χ^2	χ^2 / df	CFI	SRMS	AIC
1	-	-	-	-	-	-	.009	.201	2.916	2.916	.991	.0196	28.916
2	-	-	-	-	-	.007	.066	.223	4.285	2.143	.992	.0167	4.285
3	+	-	-	-	-	.024	.066	.223	3.647	1.824	.995	.0137	53.647
4	+	-	-	-	.032	.043	.232	.473	.825	.413	1.000	.0550	66.825
5	+	+	-	-	.050	.048	.237	.474	1.402	.496	1.000	.0052	105.402
6	+	+	+	-	.154	.056	.237	.483	1.870	2.385	1.000	.0055	127.870
7	+	+	+	+	.186	.060	.256	.493	3.030	1.5158	.999	.0053	179.030

Model 1 include having ADz as independent variable, PSQI, as mediating variable, and CESD as dependent variable. Variables added in each model: 2) pain and discomfort, 3) BMI, 4) stress, 5) substance use (i.e., alcohol and tobacco use), 6) Internet addiction test (YIAT) and 7) protective factors (i.e., physical activity as MET and SSSQ-6). Gender was entered as a control variable in all models. A plus (+) sign indicates the variables were included in the model; a minus (-) sign indicates variables were not included in the model. CFI - Comparative Fit Index; SRMR - Mean Square Residuals; AIC - Akaike Information Criterion.
ADz – current allergy or asthma; AUDIT - Alcohol Use Disorders Identification Test; BMI – Body Mass Index; CESD – Center for Epidemiological Studies Depression; FTND - Fagerström Test for Nicotine Dependence; YIAT – Internet Addiction Test; Pain – Pain / Discomfort; PSQI – Pittsburg Sleep Quality Index; MET - Metabolic Equivalent of Task; SSSQ-6 – Satisfaction with Social Support.

.001), and Internet addiction (total effect of β = .237, p < .001, direct effect of β = .087, p = .002, and indirect effects β = .150, p < .001). Being female had a significant direct and indirect effect on depression (total effect of β = .147, p < .001, direct effect of β = .045, p < .05, and indirect effects β = .102, p < .001), a direct effect on stress (β = .172, p < .001) and, through stress, female gender had indirect effects on sleep quality (β = .071, p < .001), and pain / discomfort (β = .028, p < .001). Then the seven study hypotheses were tested with Model 7:

Hypothesis 1: (ADz is significantly associated with depression only indirectly through its negative impact on sleep quality). This hypothesis was not supported, we found no direct effect of ADz on sleep (β = .037, p > .05).

Hypothesis 2: (the impact of ADz on depression is also mediated by stress and pain / discomfort). This hypothesis was supported; ADz had a direct impact on pain / discomfort (β = .068, p < .05) and stress (β = .060, p < .05) that resulted in a significant indirect effect on depression (β = .052, p < .05).

Hypothesis 3: (BMI is only indirectly associated with depression through its negative impact on sleep quality, increased pain / discomfort, and stress). This hypothesis was supported: the impact of BMI on sleep (β = .056, p < .001), and depression (β = .065, p < .05) was only indirect. Also as predicted, BMI showed significant effects on pain / discomfort (total effect of β = .131, p < .001, direct effect of β = .117, p < .001, and indirect effects β = .014, p < .05) and a small, but significant effect on stress (β = .036, p < .05).

Hypothesis 4: (higher stress is directly and indirectly associated with higher depression through its direct negative impact on sleep quality and increased pain / discomfort). This hypothesis was also supported, stress had a direct negative impact on sleep quality (β = .387, p < .001) and pain / discomfort (β = .161, p < .001). In addition, stress was directly (β = .512, p < .001) and indirectly associated with depression (β = .082, p < .001).

Hypothesis 5: (substance use is directly and indirectly associated with depression through its negative impact on sleep quality, increased pain / discomfort, and stress). This hypothesis was only partially supported. We found that high-risk drinking was indirectly associated to sleep (β = .036, p < .05), pain / discomfort (β = .017, p < .001) and depression (β = .064, p < .001) by having a negative impact on stress (direct effect β = .105, p < .001). However, contrary to our hypothesis, there was no direct impact of high-risk drinking on depression, sleep, or pain / discomfort (all paths tested, p > .05). Further, tobacco use was not significantly associated to depression or any of the mediating variables (all paths tested, p > .05) but the small direct and indirect effects of tobacco use added up to a small significant total effect (β = .072, p < .05) on depression.

Hypothesis 6: (Internet addiction is directly and indirectly associated with depression through its negative impact on sleep quality and stress). This hypothesis was only partially supported. Internet addiction had no direct impact on sleep quality, but had significant indirect and total effects on sleep quality (total effect of β = .070, p < .05, direct effect of β = −.031, p >.05, and indirect effects β = .101, p < .001). As expected, Internet addiction had a significant impact on stress (β = .287, p < .001) and depression (total effect of β = .237, p < .001, direct effect of β = .087, p = .002, and indirect effects β = .150, p < .001). In addition, Internet addiction had an unexpected positive direct impact on pain (β = −.102, p = .005), that was neutralized (total effect of β = −.056, p = .107) by the indirect effects mediated by stress (β = .046, p < .001).

Hypothesis 7: (higher levels of PA and SSSQ-6 are directly and indirectly associated with better sleep quality and less stress, pain / discomfort, and depression). This hypothesis was also partially supported. Contrary to our predictions, PA --as measured in this study-- had no measurable effect on sleep, pain / discomfort, or depression (all paths tested, p > .05). On the other hand, as predicted, SSSQ-6 was directly and indirectly associated with better sleep quality (total effect of β = −.225, p < .001, direct effect β = −.140, p < .001, and indirect effect β = −.085, p < .001) and less depression (total effect of β = −.239, direct effect β = −.102, and indirect effect β = −.150, all p < .001). Further, SSSQ-6 also had a direct effect on stress (direct effect β = −.181, p < .001) and only an indirect effect on pain / discomfort (total effect of β = −.083 p < .05, direct effect β = −.054, p = .145 and indirect effect β = −.029, p < .001).

Table 4: Regression coefficients for Model 7 including standardized direct, indirect, and total effects for the predictor variables (i.e., ADz, BMI, alcohol and tobacco use, Internet addiction, PA as MET min/ week and Social Support), the mediating variables (i.e., sleep quality; pain/ discomfort, and stress) and the outcome variable (i.e., depression). Significant effects are in bold.

| Outcome | | Predictor | Standardized Regression Coefficients: Direct, Indirect and Total Effects | | | | | | | |
			β Direct	SE	CR	p	β Indirect	p	β Total	p
PSQI		Female	-	-	-	-	.071	<.001	.071	<.001
PSQI	←	ADz	.037	.265	1.263	.263	.037	.018	.074	.032
PSQI	←	BMI	-.032	.100	-1.092	.276	.056	<.001	.024	.460
PSQI	←	Pain	.175	.259	5.85	<.001	-	-	.175	<.001
PSQI	←	Stress	.387	.119	12.089	<.001	.028	<.001	.415	<.001
PSQI	←	AUDIT	.055	.021	1.859	.061	.036	.004	.092	.004
PSQI	←	FTND	.03	.101	1.007	.333	.024	.138	.054	.098
PSQI	←	IATS	-.031	.014	-.993	.346	.101	<.001	.070	.049
PSQI	←	MET	.022	.098	.735	.472	-.015	.298	.006	.848
PSQI	←	SSSQ-6	-.140	.119	-4.635	<.001	-.085	<.001	-.225	<.001
Pain	←	Female	-	-	-	-	.028	<.001	.028	<.001
Pain	←	ADz	.068	.035	2.068	.036	.010	.048	.078	.022
Pain	←	BMI	.117	.015	3.574	<.001	.014	.010	.131	<.001
Pain	←	Stress	.161	.015	4.534	<.001	-	-	.161	<.001
Pain	←	AUDIT	-.043	.003	-1.28	.198	.017	<.001	-.026	.439
Pain	←	FTND	.048	.015	1.428	.188	.006	.294	.054	.148
Pain	←	YIAT	-.102	.002	-2.917	.005	.046	<.001	-.056	.107
Pain	←	MET	-.042	.014	-1.257	.213	-.003	.548	-.045	.192
Pain	←	SSSQ-6	-.054	.015	-1.589	.145	-.029	<.001	-.083	.022
Stress	←	Female	.172	.070	5.47	<.001	-	-	.172	<.001
Stress	←	ADz	.060	.078	1.968	.048	-	-	.060	.048
Stress	←	BMI	.086	.033	2.813	.010	-	-	.086	.010
Stress	←	AUDIT	.105	.007	3.379	<.001	-	-	.105	<.001
Stress	←	FTND	.039	.035	1.251	.294	-	-	.039	.294
Stress	←	YIAT	.287	.004	9.193	<.001	-	-	.287	<.001
Stress	←	MET	-.019	.031	-.622	.548	-	-	-.019	.548
Stress	←	SSSQ-6	-.181	.039	-5.789	<.001	-	-	-.181	<.001
CESD	←	Female	.045	.573	1.798	.036	.102	<.001	.147	<.001
CESD	←	ADz	-.019	.647	-.772	.449	.052	.014	.033	.305
CESD	←	PSQI	.146	.091	5.264	<.001	-	-	.146	<.001
CESD	←	BMI	-.025	.273	-1.033	.338	.065	.005	.040	.229
CESD	←	Pain	.132	.652	5.252	<.001	.026	<.001	.158	<.001
CESD	←	Stress	.512	.338	17.713	<.001	.082	<.001	.594	<.001
CESD	←	AUDIT	-.014	.066	-.558	.612	.064	<.001	.050	.140
CESD	←	FTND	.037	.255	1.522	.133	.035	.119	.072	.025
CESD	←	YIAT	.087	.036	3.35	.002	.150	<.001	.237	<.001
CESD	←	MET	-.019	.269	-.774	.471	-.015	.457	-.034	.317
CESD	←	SSSQ-6	-.102	.328	-4.003	<.001	-.137	<.001	-.239	<.001

ADz – current allergy or asthma; AUDIT - Alcohol Use Disorders Identification Test; CESD – Center for Epidemiological Studies Depression; FTND - Fagerström Test for Nicotine Dependence; YIAT – internet Addiction Test, Pain – Pain / Discomfort; PSQI – Pittsburg Sleep Quality Index; MET - Metabolic Equivalent of Task min / week; SSSQ-6 – Satisfaction with Social Support
β – Estimate; SE - standard error, CR – Critical Ratio, p – significance level. Dashes represent empty cells or no information because the paths were not tested in the model.

Discussion

The co-occurrence of multiple interacting medical and psychological disorders is extremely common, and the link between mood disorders, particularly depression, and allergic disease is widely accepted. Our goal was to explore the interrelations among the co-morbid conditions that previous research has linked to depression which include ADz, BMI, sleep

quality, pain/ discomfort, stress, substance use, and Internet addiction, as well as potential protective factors (i.e., PA and SSSQ-6). To asses this network of co-occurring factors and their connections, we constructed seven quantitative models and tested them using multivariate techniques (i.e., SEM), which afforded us the opportunity to examine both direct and indirect effects of variables influencing depression. To our knowledge, our exploratory study is the first attempt at identifying potential factors involved in the relation between allergic disease and depression through multivariate data modeling. We used parsimonious, evidence-based, SEM to evaluate the causal pathways linking allergic disease and depression, while accounting for multiple potential contributing factors among emerging adults. Our findings suggest that allergic disease is only one of multiple factors modulating depression. There were six factors impacting depression directly and indirectly: female gender, sleep quality, pain/discomfort, stress, Internet addiction, and SSSQ-6. ADz, BMI, and substance use also contributed to depression but only indirectly. Consistent with previous research, we found that stress was the most important contributing factor to depression. Stress impacted depression through multiple pathways: It had a direct effect on depression, but also indirect effects by having an adverse impact on sleep quality and pain / discomfort. Moreover, the effect of ADz on depression was also mediated by pain / discomfort and stress. Contrary to previous research, however, no direct association between ADz or BMI and sleep or depression was found. As with ADz, the effect of BMI on depression was indirect, associated to pain / discomfort and mediated by stress. In addition, the most important effect of high-risk drinking on depression was indirect, resulting from the effect of high-risk drinking on stress and its impact on sleep quality, pain / discomfort, and depression. As expected, Internet addiction had a significant direct effect on stress and depression. However, contrary to previous reports, the relation between Internet addiction and depression was not mediated by poor quality sleep [30,39]. Instead, Internet addiction had only an indirect effect on sleep quality mediated by stress that further exacerbated depression. Also unexpectedly, PA --as measured in this study-- had no effect on sleep, pain / discomfort, or depression. Finally, consistent with earlier literature, SSSQ-6 was associated with better sleep quality, lower stress, and less depression.

Because the interaction between participating factors is complex, studying the individual relationships between these variables is insufficient. For example, the bivariate analysis suggests that a significant correlation exists between ADz and depression. Also, the SEM models 1 and 2 (Fig 1), show a direct link between ADz, pain / discomfort, and sleep quality. Further, as in Audino's findings [91], before considering the impact of sleep and pain / discomfort, ADz appeared to be the sole independent contributor to depression. However, results from the multivariate analysis (Model 7) show a complex picture in which poor sleep quality, pain/discomfort, high stress, Internet addiction, and lack of social support interact to increase the risk for depression, while ADz, BMI, and substance use had only an indirect effect. Our findings, therefore, highlight the need to provide integrated effective care if we want to improve the quality of life of patients with multiple morbidities including allergic conditions (e.g., asthma, allergic rhinitis, allergic dermatitis) and associated comorbidities (i.e., overweight, poor sleep quality, pain/ discomfort, stress, substance use, and depression).

Multimorbidity among emerging adults

The prevalence of multimorbidity has increased recently in the general population. Both, the proportion of people affected and the number of co-occurring morbidities tend to increase with age. It has been estimated that 11.3% of adults ages 25 to 44 have at least two co-morbid physical conditions, and that 5.7% suffer co-morbid physical and mental health disorders [149]. There is evidence that co-occurring psychiatric and substance use disorders, for example, are associated with more functional impairment than either type of disorder alone [150]. Moreover, multimorbidity has a stronger negative impact in younger people [151]. During the transition into adulthood emerging adults must assume responsibilities known to impact their own well-being such as meal preparation, self-regulation of substance use, management of work and sleep routines, and in the case of students with multimorbidity, appropriate health care management. Managing multimorbidity is particularly challenging for young adults in view of the complexity and possible interactions between conditions, as well as the students' constraints of time and resources. This is of great concern given that over one third of our students were overweight or obese and one fifth of them reported suffering either asthma and/or allergy. In addition, 42.8% of the students were classified as having symptoms of depression (CESD ≥ 16). The high rate of self-reported symptoms of depression in our students is similar to that reported by children and adolescents (42.8% vs. 20 - 50%) in epidemiologic studies [152] and similar to estimates using the CESD in college populations (36.8%, 95% CI, 35.2–38.4) [153]. Further, more than two-thirds of the students reported experiencing poor sleep quality (PSQI > 5), and only 25.2% reported the recommended eight or more daily hours of sleep. These findings are consistent with evidence from the literature showing changes in sleep architecture during adolescence and early adulthood resulting from both social and biological factors [140]. The evidence suggests that during this period of susceptibility, inadequate sleep can trigger a cascade of negative health events, including depression. College counseling centers report a significant increase in the number of students seeking mental health services, as well as worsening of the severity of their conditions [26,154,155]. There is evidence that the self-rated emotional health of college students has been declining [26]. For instance, about half of the college students report feeling so depressed "that it was difficult to function," and experiencing "overwhelming anxiety," and high levels of stress [27]. Finally, students with ADz experienced more pain / discomfort, worst sleep quality, and more depression.

In addition, alcohol consumption has continued to increase in the US among all age groups [156], but young adults have consistently had the highest prevalence of alcohol use (80.1%), high-risk drinking, and dependence than any other group [156,157]. It is estimated that roughly one fifth of alcohol users ages 18-29 meet DSM – IV criteria for alcohol use disorder

[156,157]. For college students, drinking is a rite of passage, part of the college experience [158]. Findings in our study show drinking patterns comparable to those obtained in national surveys, with most students reporting past-month drinking (70.2% vs. 63.2%), forty percent (40.2% vs. 37.9%) past-month binge drinking [159], and roughly one fifth indicating possible alcohol dependence [156,157]. Positive alcohol expectancies are associated to increased drinking [160], particularly in a college setting [158,161]. For example, college drinkers reported both positive and negative consequences from drinking, but most (96.6%) reported at least one positive consequence such as "having a good time" and "feeling less stressed", while 82% of drinkers reported at least one negative consequence [161]. The authors noted that positive consequences were associated with lower levels of drinking, a pattern not necessarily perceived by the students [161]. This mixed experience among drinkers may explain why drinking in this population does not appear to be directly related with depression. Cigarette smoking has changed significantly in the last decades [162]. Consumption of cigarettes has decreased significantly overall, and light smoking and smoking e-cigarettes have become the predominant forms of tobacco use among young adults [163]. The prevalence of smoking among our study participants was quite low (5.4%) and most smokers were classified as light smokers (i.e., < 10 cigarettes a day). Although occasional smoking and light smoking were previously considered transient behaviors, they are now a common social practice for college students [164]. There is some evidence suggesting that social-light-smoking (i.e., smoking primarily in social contexts) may be growing among college students [164]. Interestingly, even though tobacco use was not -directly or indirectly- associated to depression or any of the mediating variables in this study, it had a significant total effect on depression, which suggests that tobacco use has an effect on depression but it is difficult to detect in these data.

The role of the Internet in the lives of young adults is clear. According to the Pew Center, among 18- to 29-year-olds, 39% are connected online almost constantly and 49% go online multiple times per day [165]. Almost all of the students in our sample had an account in Facebook or other social networking site. This ubiquitous use has consequences for the day-to-day lives of young adults. About one fifth of the students had an YIAT score suggestive of problematic or pathological Internet use [145]. Scientific evidence regarding the impact of internet use on the mental health of teens and young adults has been mixed [166]. It has been argued that the impact of online communication varies depending on the quality of the offline social network: that is, online communication with close friends and family enhances psychological well-being, while internet communication with weak social ties might not [167]. Research looking into the quality of friendships and social support as predictors of internet problematic use supports this explanation [168-170]. We found a significant negative correlation between Internet addiction and perceived social support that suggests that this might also be the case among our students; in addition, together these two factors impacted depression. Lack of social support was a key factor predicting

depression in our population, which is consistent with research evidence showing that social support improves well-being [36,37,111,112]. Consistent with Wang et al., [111] we found that social support regulated the effect of stress on depression.

Finally, about one fourth of our students (25.5%) reported engaging in recommended levels of physical activity (> 1500 MET min/week). However, we found no effect of PA on any of our outcome variables (i.e., sleep, pain / discomfort, stress, depression). There is some evidence suggesting that it is leisure-time physical activity [171], or even light PA (as pleasant activation) [172], rather than the energy expenditure of physical exercise that impact well-being. This bring us back to the importance of social support in modulating depression. Pickett et al [171]. Found that higher levels of leisure-time PA, but not non-leisure time PA were significantly associated with lower depression. Unfortunately, our data do not allow us to differentiate between leisure and non-leisure PA. Thus, this question remained unanswered.

Conclusions

This is the first attempt at identifying potential factors involved in the relation between ADz and depression using multivariate data modeling to evaluate the causal pathways linking the two conditions, while accounting for multiple potential contributing factors (i.e., sleep quality, pain/discomfort, BMI, stress, substance use, Internet addiction, physical activity, and SSSQ-6) among emerging adults. Our results are consistent with previous research, suggesting that allergic disease is only one of multiple factors modulating depression. Although the mechanisms underlying these relationships remain elusive, there is evidence showing that inflammatory processes can be the underlying physiological mechanism linking many of these conditions including Adz [172,174], obesity, stress, pain / discomfort, poor sleep quality, and depression [175]. Research exploring the underlying factors linking inflammatory processes to behavioral outcomes suggests that inflammatory processes and social behavior regulate one another. Proinflammatory cytokines aid in coordinating the body's response to illness, injury, or infection. *Sickness behavior* is part of this coordinated response of the organism to conserve energy and support recovery. Sickness behavior includes a constellation of symptoms such as fatigue, increased pain, anhedonia, loss of appetite, and social withdrawal or loss of interest in social activities. Multiple pathways have been suggested to explain how peripheral immune activation induces sickness behavior. These include increases in endotoxin and proinflammatory cytokine IL-6 production that can lead to increases in neural sensitivity, particularly to social stressors [176]. Thus, socially isolated individuals tend to have increased levels of inflammation that further exacerbates inflammatory responses to other social stressors [177]. Sickness behavior in patients with chronic inflammatory disorders (e.g., allergic disease, pain, and obesity) may lead to hypersensitivity to social stressors (e.g., isolation and discrimination) increasing their risk for depression [176]. These factors may tart an interdependent uncontrolled cycle where chronic inflammatory conditions → social hypersensitivity → heightened stress responses →

increased social withdrawal → increased inflammation → increased depression exacerbation of chronic conditions, and so on. Following this rationale, research could be conducted to determine if anti–inflammatory medications can impact symptoms of depression, for example. In a recent clinical trial, investigators showed a significant benefit of low dose buprenorphine on suicidal ideation; however, the benefit on depression was smaller and not statistically significant. Nevertheless, this is a promising finding for the treatment of depression that warrants further research [178].

Limitations

Although mediation analysis assumes both causal and temporal relations, the proposed mediation pathways require further testing with prospective studies on a clinical population with ADz. Only prospective studies can establish the true nature of the association between the network of comorbidities included in this study, and answer with certainty whether the interactions among these factors increase the risk for depression among patients with ADz. Additionally, it is possible that age–related paths and trajectories may modify these relationships.

Our study was based on self–reported data and is, hence, susceptible to bias. The characteristics of the study participants, college students, limit the generalizability of our findings. Finally, we did not collect detailed information on current symptoms of ADz, so, we cannot rule out the possibility that our findings might be due to other extraneous variables or chance.

Acknowledgment

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