



**THE USE OF E-CIGARETTES AMONG CHILDREN AGED 13-18 AND THEIR
POSSIBLE EFFECT ON THE DEVELOPMENT OF DEPRESSION**

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ABSTRACT

Since they first hit the market in 2004, electronic cigarettes (e-cigarettes) have presented a global health hazard to the adolescent population. They inflict multi-organ damage to the body, and cause lasting addiction. **Purpose of Study:** To determine if there is a link between e-cigarette usage in adolescents and its possible effect on the development of depression. **Research objectives:** To determine if there is any possible trends in e-cigarette usage and reported depression. To compare between e-cigarette and c-cigarette in terms of their potency to cause depression. **Results:** E-cigarette usage in the adolescent population is positively correlated with depression with an overall Odds Ratio (oOR) of 1.63 [95%CI 1.17, 2.26]. When filtered for studies with data on multiple distinct age groups, the 8th grade/14 year old demographic had the highest likelihood of depression in every tested category (exclusive e-cigarette, exclusive c-cigarette, and dual usage). When filtered for comparable studies exclusive e-cigarette usage was found to be less likely to cause depression (oOR)=1.41 [95%CI (1.15, 1.72)] than exclusive c-cigarette usage oOR= 2.31 [95%CI (1.77, 3.01)] or dual usage 2.22 [95%CI (1.73, 2.85)]. **Conclusion:** The literature review indicated a positive correlation between e-cigarette usage and depression in adolescents. The younger teens are more likely to be affected due to the effect of nicotine on the developing brain. The older population is converting to exclusive c-cigarette and dual usage perhaps as a method of self-medication.

KEYWORDS: “Electronic cigarettes”, “Vaping”, “Tobacco”, “Adolescent”, “Depression”, “Mentalhealth”

INTRODUCTION

Introduced in 2004, Electronic Nicotine Delivery Systems (ENDS) commonly known as e- cigarettes or vape-pens were presented as a new, less dangerous alternative to combustible cigarettes (c-cigarettes). In addition, the nicotine containing fluid came in a variety of flavors that should appeal to many consumers. It soon became apparent that the flavors including bubble gum, birthday cake and strawberry were aimed at the youth market.^[1] Vaping has since imbedded itself into youth culture with many references to the act saturating user created media on sites such as YouTube.^[2] According to bellwether complaints from the ongoing JUUL litigation, children as young as 12 are using their product.^[3]

As with any new drug technology, research lags behind, but current studies are showing that the glycerin in the e-cigarette breaks down into aldehydes which reacts with glutathione reductase decreasing its ability to reduce NADPH. This in turn leads to an increase in NADPH oxidase which produces reactive oxygen species (ROS).^[4] These cause multi-organ damage throughout the body, most concerning the lungs^[5,6] heart^[7,8,9] and brain.^[9]

Most of the programs to prevent vaping in the teen demographic are focused on this aspect of the activity, presenting the damage as purely physical. However, there is another hazard that should not be overlooked. Studies performed on South Korean college students showed increased depression and suicidal ideation in ENDS users.^[10] If this finding is an indication of the possible mental effects in adolescents, a group already at risk for depression and suicide^[11], then the treatment thereof must change on a fundamental level. It must be approached as a mental affliction as well as a physical addiction. In addition, depression has been shown to directly affect the academic performance of students.^[12] In short, significant depression secondary to vaping may cause repercussions in the academic career of the student. Beyond that, verifying a mental effect of the ENDS can focus further studies on its effects on brain chemistry. This will help identifying and litigating against the offending chemicals, further protecting not only the youth, but all ENDS users: a market reportedly valued at \$44.6 million.^[13]

Purpose

This study seeks to determine if there are a link between e-cigarette usage in adolescents and its possible effect on

the development of depression.

Research objectives

- To determine if there is any possible trends in e-cigarette usage and reported depression.
- To compare between e-cigarette and c-cigarette in terms of their potency to cause depression.

MATERIALS AND METHODS

Data sources

PubMed and GoogleScholar were searched using the keywords “E-cigarette”, “Vaping”, “Vape”, “Adolescent”, “Teen”, “High school”, and “Depression”

Eligibility criteria

Only studies in English and with texts and results available through Open Access were considered. Dates included were 2008 to present. Studies had to be longitudinal or cross-sectional with participants aged 13-18, differentiate between c-cigarettes, nicotine containing e-cigarettes and Tetrahydrocannabinol (THC)-containing e-cigarettes, and include a depression survey such as Center for Epidemiological Studies Depression Scale (CES-D-10).

Extraction

Tools on covidence.org.^[14] were used to screen papers and create the PRISMA Flowchart. Calculations, Risk of Bias Diagram and Forest Plots were created using Review Manager (RevMan).^[15]

Risk of bias assessment

Bias was assessed using the Analytical cross sectional studies Critical Appraisal Tool created by Moola^[17] which consisted of 8 questions.

1. Were the criteria for inclusion in the sample clearly defined?

2. Were the study subjects and the setting described in detail?
3. Was the exposure measured in a valid and reliable way?
4. Were objective, standard criteria used for measurement of the condition?
5. Were confounding factors identified?
6. Were strategies to deal with confounding factors stated?
7. Were the outcomes measured in a valid and reliable way?
8. Was appropriate statistical analysis used?

Statistical analysis

Data of depression in e-cigarette users were extracted as odds ratios, or calculated as size of effect and converted to odds ratios as detailed in Cochrane Handbook.^[17] Data were then entered into RevMan and converted to log odds ratios and used to create a forest plot.

RESULTS

56 full text articles were screened for eligibility. Of those, 34 were found to be irrelevant and 17 were excluded for having an adult population, not presenting depression data for sole e-cigarette use, or not differentiating e-cigarette use from other forms of nicotine/THC use. In the end 5 studies were chosen consisting of 3 American, 1 Norwegian, and 1 Taiwanese study. A total of 47,300 participants between the ages of 12 and 18 were included with a weighted mean age of 15.4. Figure 1 is the PRISMA flow diagram. The background information of the papers is listed on Table 1. Table 2 shows all the standardized ratios for all included groups including exclusive c-cigarette users and dual users from the studies that expressed that data independently: Chen 2019^[18] Gorfinkel 2022,^[19] and Lechner 2017.^[20]

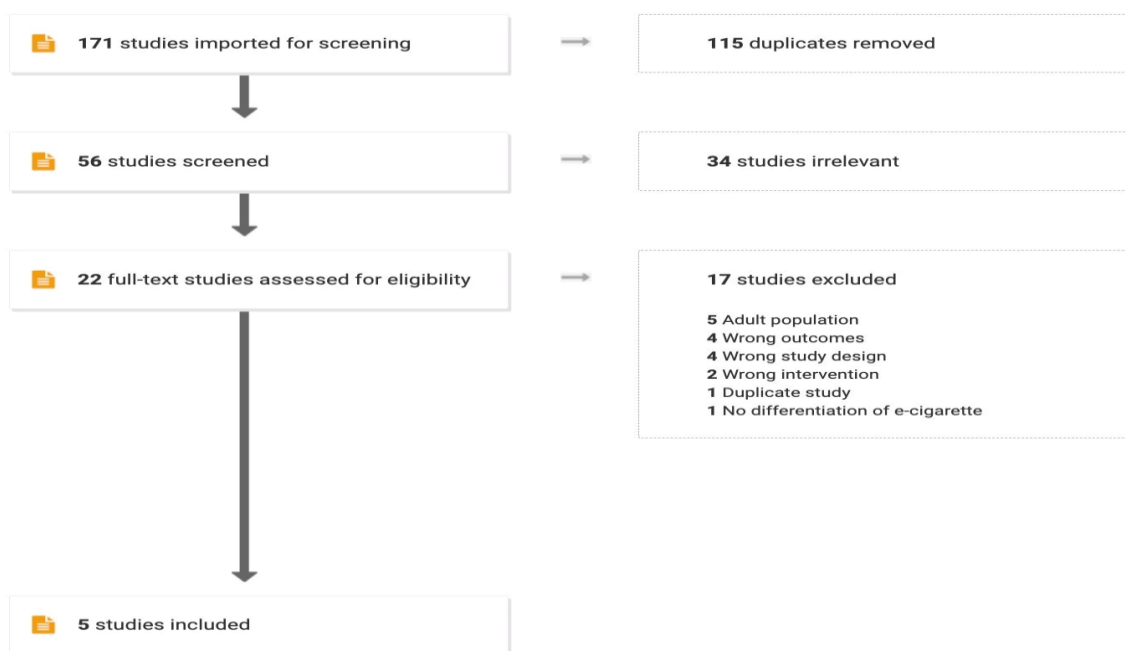


Figure 1: Prisma flowchart.

Table 1: Cited papers.

Author(year)	Study Type	Location	Date of Study	Source of Data	Adolescent Sample Size N=44,861	Age Range (Mean)
Audrain-McGovern 2022 ^[21]	Cohort, Longitudinal	Philadelphia, PA	2018-2019	Paper and pencil survey	1,808	14-15 (14.5)
Chen 2019 ^[18]	Cross- sectional, retrospective	Taiwan	Jul-Dec2014	National Survey of Substance Use	2,726(12-15) 1,719(16-17)	12-17(13.5,16.5)
Gorfinkel 2022 ^[19]	Cross- sectional, retrospective	US nationwide, Lead by University of Michigan	2017-2018	Monitoring the Future Study	32,636	13-18 (13.5, 15.5, 17.5)
Lechner 2017 ^[20]	Cross- sectional, Longitudinal	Los Angeles	2013-2014	Web survey of high schools in LA	2,460	(14.1 [SD=0.41])
Tokle 2022 ^[22]	Cross- sectional, Longitudinal	Norway	2017(T1), 2018 (T2), 2019(T3)	Monitoring Young Lifestyles (MyLife) Study	3,512	13-17 (14.2,15.0,16.2)

Table 2: Odds Ratios of depression in all users divided by group.

Study Group	aOR (95% CI)	log(OR)[SE]	Study Group	aOr (95%CI)	Log(OR)[SE]
Audrain- McGovern 2022	1.01 (0.97,1.05)	0.01 [0.02]	Gorfinkel 2022 12th grade D	1.81 (1.05, 3.12)	0.59 [0.28]
Chen 2019	2.20 (0.50, 12.3)	0.79 [0.76]	Lechner 2017 any use	1.37 (0.86, 2.16)	0.31 [0.23]
Chen 2019 CC	2.20 (1.10, 4.40)	0.79 [0.35]	Lechner 2017 sustained use	1.39 (0.80, 2.39)	0.33 [0.28]
Chen 2019 D	3.1 (1.1-15.5)	1.13 [0.53]	Lechner 2017 CC	2.38 (1.46, 3.88)	0.87 [0.25]
Gorfinkel 2022 8th grade	2.01 (1.46, 2.77)	0.69 [0.16]	Lechner 2017 D	1.72 (1.06, 2.81)	0.54 [0.25]
Gorfinkel 2022 10th grade	1.20 (0.97,1.49)	0.18 [0.11]	Tokle 2022 Baseline	5.40 (4.23, 6.90)	1.69 [0.13]
Gorfinkel 2022 12th grade	1.20 (0.84,1.70)	0.18 [0.18]	Tokle 2022 Baseline NN	1.22 (0.96, 1.54)	0.20 [0.12]
Gorfinkle 2022 8th Grade CC	3.52 (1.94, 6.39)	1.07 [0.33]	Tokle 2022 T2/T3	1.87 (1.45, 2.40)	0.63 [0.13]
Gorfinkel 2022 10th grade CC	2.26 (1.51, 3.38)	0.83 [0.27]	Tokle 2022 T2/T3 NN	1.69 (1.33, 2.14)	0.52 [0.12]
Gorfinkel 2022 12th grade CC	1.81 (1.05, 3.12)	0.54 [0.37]	CC:Exclusive C-Cigarette Usage		
Gorfinkle 2022 8th Grade D	3.52 (1.94, 6.39)	1.26 [0.30]	D: Dual Usage		
Gorfinkel 2022 10th grade D	2.26 (1.51, 3.38)	0.82 [0.21]	NN: Non-Nicotine E-Cigarette Usage		

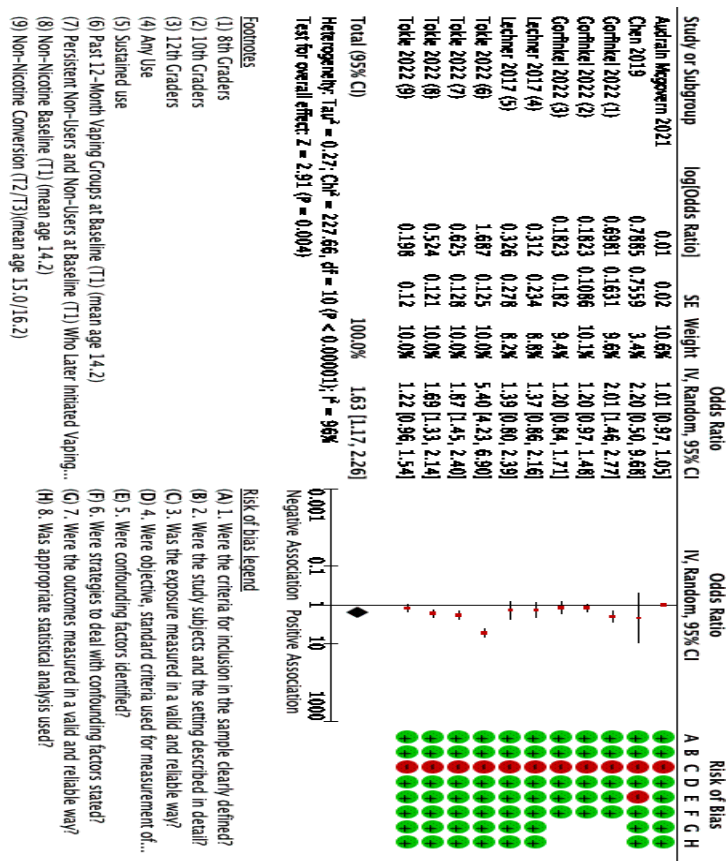
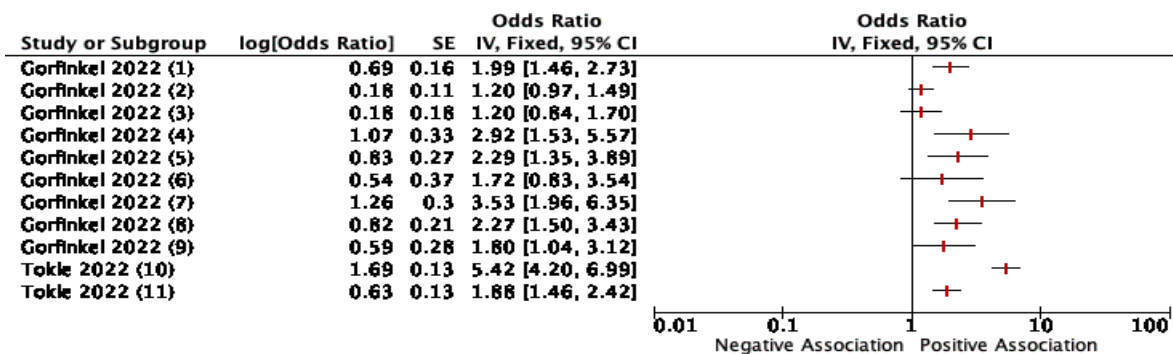


Figure 2: Odds Ratios for Depression in Exclusive E-Cigarette Usage in All Available Papers with Risk of Bias.

The forest plot in Figure 2 shows that exclusive e-cigarette users have an increased chance of being depressed than non-users with an overall odds ratio (oOR) of 1.63 [95% CI (1.17,2.26)]. This is confirmed to be statistically significant with a test for overall effect equal $Z=2.91$ ($p=0.004$). The Risk of Bias (RoB) shows

that while the papers are overall of low risk, they are all high risk in the matter of calculating exposure as they rely on self reporting. The missing data for Gorfinke! 2022 is because the full paper was not available on OpenAccess. Data was extracted from that available in the free abstract.



Footnotes

- (1) 8th grade e-cigarette usage
- (2) 10th grade e-cigarette usage
- (3) 12th grade e-cigarette usage
- (4) 8th grade c-cigarette usage
- (5) 10th grade c-cigarette usage
- (6) 12th grade c-cigarette usage
- (7) 8th grade dual usage
- (8) 10th grade dual usage
- (9) 12th grade dual usage
- (10) Past 12-Month Vaping Groups at Baseline (T1) (Mean Age 14.2)
- (11) Persistent Non-Users and Non-Users at Baseline (T1) Who Later Initiated Vaping (T2/T3) (Mean Age 15.0/16.2)

Figure 3: Odds Ratios of Depression in Exclusive E-Cigarette Usage, Exclusive C-Cigarette Usage and Dual Usage From Papers that Included Age Specific Data.

Figure 3 contains only data from the two papers that contained data divided into multiple distinct age groups. This data shows that the youngest group (8th graders/14 year olds) had the highest likelihood of depression in every grouping. The most statistically significant difference is seen in e-cigarette users. This is shown in group Gorfinkel 2022 8th grader's OR of 1.99 [95% CI

(1.46,2.73)] vs 10th grader's OR of 1.20 [95%CI 0.97, 1.49][20], and Tokle 2022 Baseline (T1) (mean age 14.2) with an OR of 5.42 [95%CI (4.20, 6.99)] vs (T2/T3) (mean age 15.0/16.2) with an OR of 1.88 [95%CI (1.46, 2.42)].

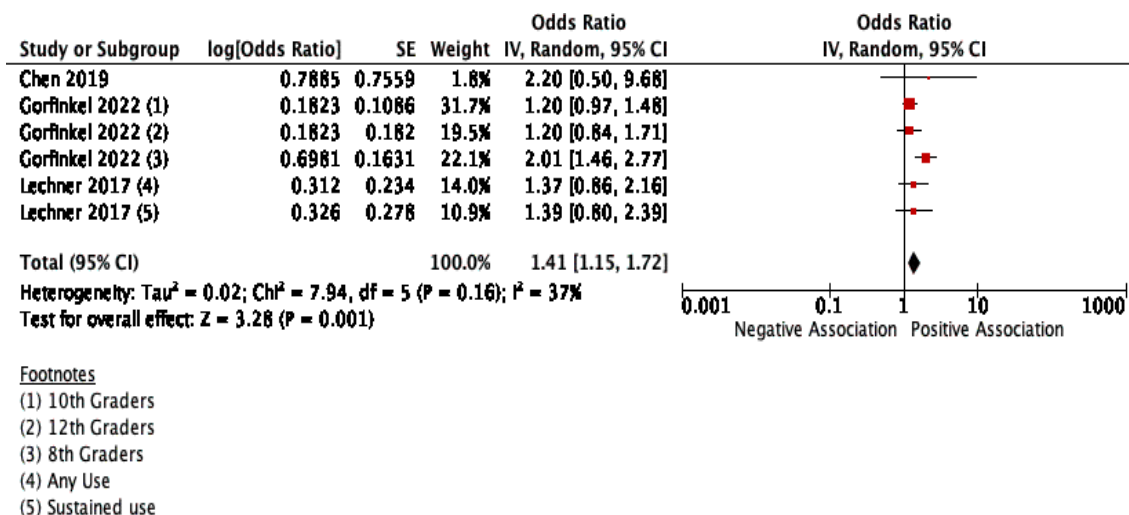


Figure 4: Odds Ratios of Depression in Exclusive E-Cigarette Usage From Papers That Included Comparison Data for Exclusive C-Cigarette Usage and Dual Usage.

Figure 4 contains data only from papers that included comparison data on exclusive e-cigarette use, c-cigarette use and dual usage. This forest plot shows that exclusive e-cigarette users are more likely to be depressed than

non-users with an overall odds ratio of 1.41 [95% CI (1.15,1.72)]. This is statistically significant with Z=3.28 (P=0.001).

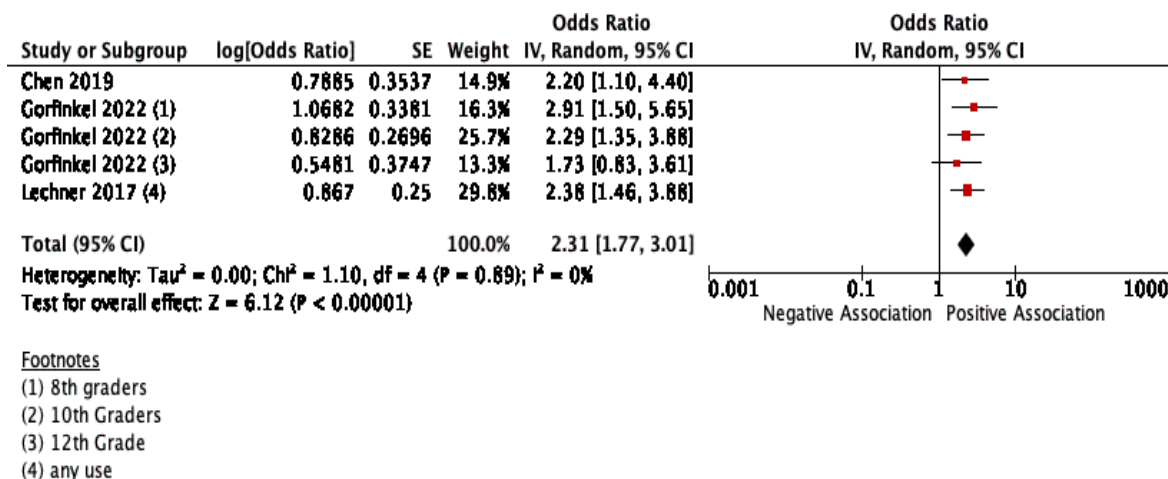
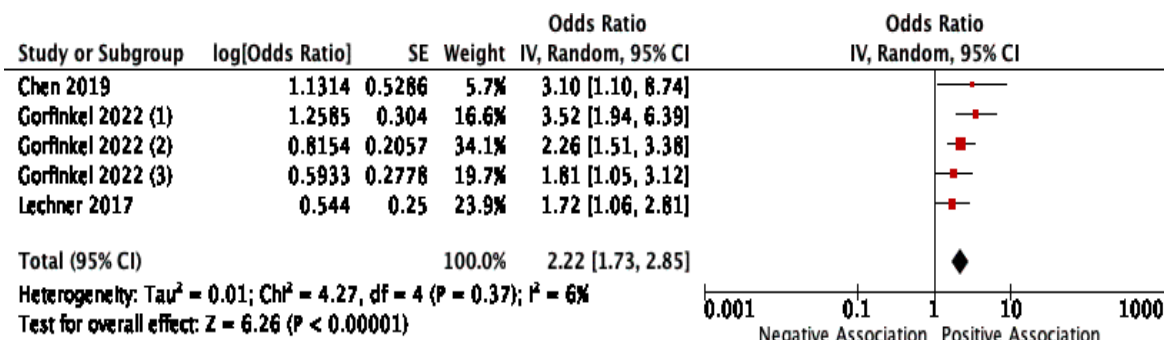


Figure 5: Odds Ratios for Depression in Exclusive C-Cigarette Users From Papers That Included Comparison Data for Exclusive E-Cigarette Usage and Dual Usage.

Figure 5 contains data only from papers that included comparison data on exclusive e-cigarette use, c-cigarette use and dual usage. This filtered forest plot shows that exclusive c-cigarette users are more likely to be

depressed than non-users with an overall odds ratio of 2.31 [95%CI (1.77, 3.01)]. This is statistically significant with Z=6.12 (P<0.00001).



Footnotes

(1) 8th Grade

(2) 10th Grade

(3) 12th Grade

Figure 6: Odds Ratios for Depression in Dual Users From Papers That Included Comparison Data for Exclusive E-Cigarette Usage and Exclusive Cigarette Usage

Figure 6 contains only data from papers that included comparison data for exclusive e-cigarette usage and exclusive c-cigarette usage. This filtered forest plot shows that dual users are more likely to be depressed than non-users with an overall odds ratio of 2.22 [95%CI (1.73, 2.85)].

This is statistically significant with $Z=6.26$ ($P<0.00001$).

A. Overall Odds Ratio for Exclusive E-Cigarette Use

The overall OR for exclusive e-cigarette use associated with depression in adolescents is 1.63 [95%CI 1.17,2.26]. This data is statistically valid with a test for overall effect $Z=2.91$ ($p=0.004$). Figure 2 shows the forest plot for this data set with Risk of Bias (ROB) for the included studies. Forest Plot created using RevMan.

B. Effect size by age

Two of the included studies divided their data by age, Gorfinkel 2022 and Tokle 2022. Their datapoints plotted in Figure 3 show that the 14 year old/8th grade demographic had the highest likelihood of depression in every grouping (Exclusive e-cigarette usage, exclusive cigarette usage and dual usage). The most statistically significant difference is seen in e-cigarette users.

This is shown in Gorfinkel 2022 8th grader's OR of 1.99 [95%CI (1.46, 2.73)] vs 10th grader's OR of 1.20 [95%CI 0.97, 1.49], and Tokle 2022 Baseline (T1) (mean age 14.2) with an OR of 5.42 [95%CI (4.20, 6.99)] vs (T2/T3) (mean age 15.0/16.2) with an OR of 1.88 [95%CI (1.46, 2.42)].

Comparison between usage groups

Three included studies divided their data by exclusive e-cigarette, exclusive c-cigarette and dual usage groups allowing comparison. When the data was filtered to compare only these studies, depression associated with exclusive e-cigarette usage overall Odds Ratio (oOR)=1.41 [95%CI(1.15, 1.72)] was significantly lower than exclusive c-cigarette usage oOR= 2.31 [95%CI

(1.77, 3.01)] and dual usage oOR= 2.22[95%CI (1.73, 2.85)]. There was not any significant difference between exclusive c-cigarette usage and dual usage. Figures 4, 5, and 6 are the relevant forest plots.

DISCUSSION

A. Overall Odds Ratio of E-Cigarette Associated Depression

With a oOR of 1.63 [95%CI 1.17,2.26], this data clearly shows that depression is in fact associated with e-cigarette usage in adolescents. However, when the population is looked at as a whole, the effect could be quite small. What should not be ignored, however, is that the effect is supported by data from multiple countries with vastly different cultures, which filters out any region-specific causes behind the association. Whatever this effect is caused by, it is region- independent and manufacturer-independent as the US and foreign countries have different laws regulating the concentration of nicotine and the flavors allowed in e-cigarettes.

Due to the cohort design of the included studies, it is impossible to determine the direction of the association directly. However, by looking at the trends presented within the data and that contained within comparable papers, a hypothesis can be formed. Gorfinkel 2022 8th grade and Tokle 2022 Baseline (T1) data shows that age group, 8th and 9th grade, is significantly more likely to be depressed while using e-cigarettes. This finding is backed up by a Michigan study which showed "greater depressive symptoms at age 14 years old [were associated] with a faster rate of e-cigarette escalation"^[23] According to the Monitoring the Future Survey, 8th graders have always been the least likely to use e-cigarettes.^[24] In addition, according to the Global Burden of Disease Survey (GBD 2019), the 10-14 age bracket is significantly less likely to be depressed than the 15-19 age bracket in nearly every country and year since 1990^[25] So, a group that is less likely to partake and less likely to be depressed has a higher chance to be depressed while using e-cigarettes. This points to an

underlying confounding variable.

Unfortunately, the data currently available to this study does not have any divided data on age groups younger than 8th grade, but it is hypothetically probable that the younger the participant the larger the effect would be. Firstly, the immature brain is also more susceptible to the addictive affects of nicotine.^[26,27] Secondly, it has been shown that e-cigarette vapor breaks down to aldehydes which damages the frontal lobe through phagocytic NADPH Oxidase (NOX 2) activation which could cause labile mood and depression.^[4,28]

B. Exclusive E-Cigarette Use vs C-Cigarette and Dual

This hypothesis does however not explain the fact that exclusive e-cigarette use has a lower oOR 1.41 [95%CI (1.15, 1.72)] than exclusive c-cigarette usage 2.31 [95%CI (1.77, 3.01)] or dual usage 2.22[95%CI (1.73, 2.85)]. According to *Public Health Consequences of E-Cigarettes*, e- cigarettes are lower in nicotine concentration overall than c-cigarettes.^[28] So, if it were a direct nicotine to depression relationship as seen here, the older demographic should have a higher OR. This would seem to indicate that there is another factor at work. It may be that older students with depression are choosing to increase their nicotine intake as a form of self medication.^[30] The conversion is supported by a study by Choi and Bernat which noted that students who used e-cigarettes were 3.6 times more likely to convert to c-cigarettes than those who had never used e-cigarettes.^[31] Audrain-McGovern 2022 supports this: “A standard deviation increase in depression at baseline resulted in a 0.70 standard deviation increase in the rate of e-cigarette escalation across the 30-month follow-up.” According to Williams et al., “Escalating poly- substance use is associated with depression among males”^[32]

C. Limitations

There are multiple limitations that hinder this work. First and foremost, the subject of study is an illegal act when performed by a minor. This immediately limits the number of studies that will be performed due to ethical concerns. However, this is offset by the fact that the studies that do get permission have very large populations which grants them power. In this meta-analysis, it should be noted that while there are only 5 studies included there is one outlier as far as population, Gorfinkel 2022, with approximately 31,000 participants.

The second issue stemming from the illegal nature of the topic is that, given the studies rely upon self reporting of the act, it is likely to be underreported. This is likely a factor in the Chen 2019 paper where, out of a population of approximately 4,100 participants, only 34 reported e-cigarette use.

A third limitation stems from the cohort design of the included studies. This limits the scope of this meta-analysis to correlation and not causative direction.

Though it should one noted that Audrain-McGovern 2022 and Tokle 2022 are longitudinal studies, but the study designs were focused on increase in usage so that portion of the studies were not fully applicable.

The next limitation is that all the participants are minor's, and thus require parental permission to enter into a study. This could easily skew the result as parental involvement in a minor's life can have large effects on drug risk and mental state.^[33]

Another limitation is not having access to the raw data, several studies were performed on the correct population and studied the desired effects, however they presented their findings in such a way as to preclude the extraction of direct OR of vaping associated depression. One such study was Williams 2021 which consisted of approximately 51,000 adolescents who were tested for vaping and depression. Unfortunately, the data was presented for non-use, dual use, and poly use only.^[34]

Next is the limitation of the newness of the studied technology. What few longitudinal studies could be found were of short length, roughly 3-4 years. While this has allowed researchers to investigate trends of drug use, long term effects may not appear within that time frame.

Finally, only papers in English and with full text available through OpenAccess were included. One exception to this was made regarding Gorfinkel 2022 as the requisite data was available for extraction in the abstract. However, this does mean that a full risk of bias assessment for Gorfinkel 2022 cannot be made at this time. There are several countries that are performing studies on vaping including Poland and Korea, but their papers could not be searched given the criteria.

SUMMARY AND CONCLUSION

The purpose behind this meta-analysis was to discover if, in fact, e-cigarette usage in adolescents was associated with depression. The newness of the technology has limited the number of studies that have been performed. Given the nature of the act, a majority of these focused on the physical detriments it could inflict upon the body. It has been shown that oxidative stress linked to e-cigarette usage can lead to damage to the lungs, heart and brain. All of this information is indispensable in helping prevent morbidity and mortality connected with this newest addiction.

However, it is important not to ignore the invisible symptoms that have an immediate impact on the lives of adolescents. Depression is a serious and all too often deadly disorder.

5 papers with a total of 44,861 participants aged 12-18 were included in the meta analysis. Final calculations showed that the adolescent population surveyed was shown to have a positive association between depression and vaping with an overall odds ratio of 1.63 [95%CI 1.17,2.26]. This is a significant finding in that it can

immediately be used to diagnose and treat the depressed adolescent. Early identification in depression cases can allow the patient to receive proper mental therapy in a timely manner. This takes time, resources and training in order something that many school staffs have in short supply. Using this link between e-cigarette use and depression, regardless of its direction, educators have a visible indicator of this disorder. Though the adolescent will try to hide this activity, an object is much easier to find and identify than a trend in the student's behavior. Programs can thus be set up to corral e-cigarette users into a place where they can be properly treated.

Regarding the future of this path of study, there appears to be two factors affecting e-cigarette associated depression. There is the possible effect of nicotine on the immature brain inducing depression, and the self-medication of depression with ever-increasing doses and types of nicotine in older adolescents. These factors can be differentiated from each other and any other confounding factors by a longitudinal study focused on a class of students as they progress from junior high through high school. The process of studying this particular activity will always be fraught with problems due to ethical concerns and the fact that the technology and products are constantly being upgraded and changed in order to be as profitable as possible ahead of new laws. Fads and trends regarding a popular brand will always be changing, but every new study will add information to allow proper understanding of this new technology in all its capacity. Some of these may be inherited problems of nicotine, but others will be new by-products of the glycerin. Regardless of their origin, it can be stated that e-cigarettes are linked to disorders of the lung, heart, brain and now, definitively, mood.

ACKNOWLEDGEMENTS

This work is dedicated firstly to my beloved daughter, Gwendolyn. I do this to help brighten the world you will inherit. Secondly, I must thank my fiancé Sherry for putting up with my insanity and making sure I ate and slept.

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