



Original Research

## The Association of E-Cigarettes with Hypogonadism in Adult Men in Denpasar

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### Abstract

*A decrease in testosterone level can cause a set of symptoms forming a clinical syndrome called hypogonadism. One of the factors that is known to disrupt testosterone levels is smoking habits. Currently, the use of e-cigarettes as an alternative product to conventional cigarettes is increasing rapidly in many countries, including Indonesia. The amounts of harmful substances in e-cigarette aerosols are similar to the smoke produced by conventional cigarettes, but the health hazards of e-cigarettes are still not well known. This study was conducted to determine the relationship between e-cigarettes and hypogonadism in adult men in the city of Denpasar. This study uses a descriptive-analytical method in the form of a cross-sectional study. The research sample consisted of 49 e-cigarette users collected using consecutive sampling techniques. The data were then analyzed using SPSS® version 26. Based on the research obtained from the ADAM score from a total of 49 samples, the prevalence of hypogonadism is higher in the group of people who smoked e-cigarettes, about 35.3%. Overall, this study found a fairly high prevalence of hypogonadism (26.5%) in Denpasar. The chi-square test shows a p-value of 0.032 and a prevalence ratio (PR) of 5.294. Active use of e-cigarettes showed a significant association with the incidence of hypogonadism experienced by adult men in Denpasar. Based on the PR calculation, the risk of hypogonadism in active e-cigarette users was 5.294 times higher than that of adult men who were not active e-cigarette users.*

## 1. Introduction

The number of users of e-cigarettes is increasing rapidly every year. This also aligns with the number of new e-cigarette stores that keep on opening and expanding in numbers. This phenomenon shows a high demand for e-cigarettes among people<sup>[1]</sup>. The surveys conducted by Global Adult Tobacco Surveys in 2021 on 15-year-olds or older show that the number of e-cigarette users in Indonesia has reached 6.2 million adults or about 3.0% of the total population<sup>[2]</sup>. A survey in 2018 showed that as many as 6.8% of the population in Denpasar City are e-cigarette users and this percentage is known to be twice as high among teenagers<sup>[1]</sup>.

E-cigarettes are defined as devices that produce aerosols by heating certain substances in liquid form and inhaled as aerosols by the users<sup>[3]</sup>. E-cigarettes are often misinterpreted and considered safer than conventional cigarettes. The negative impacts caused by the use of e-cigarettes are very diverse, affecting a lot of different organs<sup>[4],[5]</sup>. This type of cigarette heats a liquid that contains chemicals such as glycerol, and flavorings, and most of the time includes nicotine<sup>[6]</sup>. Study shows that exposure to these chemicals for a certain period results in a decrease in testosterone and estradiol levels<sup>[7],[8]</sup>.

Hypogonadism is a clinical syndrome caused by testosterone concentrations or sperm levels not reaching concentration<sup>[9]</sup>. Based on its etiology, hypogonadism can be divided into 2 types, namely primary (hypogonadotropic) hypogonadism, and secondary (hypogonadotropic) hypogonadism<sup>[10]</sup>. Based on time of occurrence, hypogonadism can be further divided into 2 types, namely congenital hypogonadism and late-onset hypogonadism (LOH)<sup>[11]</sup>. Late-onset hypogonadism often goes undiagnosed because it does not always cause significant symptoms and signs<sup>[12]</sup>.

The associations between e-cigarette use and hypogonadism are thought to be due to several factors. One of the main factors that cause this hormonal imbalance is reactive oxygen species (ROS)<sup>[13]</sup>. Increased ROS in the body can cause health problems, one of which is in the Leydig cells<sup>[14]</sup>. This impact will disrupt the steroidogenesis process and lead to inhibited testosterone production<sup>[15]</sup>. Halted testosterone production will cause a decrease in testosterone levels in the body which will manifest clinically into the syndrome of hypogonadism<sup>[16]</sup>.

Based on the background presented, this study aims to find if there is a relationship between active e-cigarette use and hypogonadism in adult men in the Denpasar. This study is expected to serve

information about the danger of e-cigarettes in reproductive health.

## 2. Method

This study is an observational analytic study with a cross-sectional design. Data collection is conducted at e-cigarette stores spread across the city of Denpasar including its four districts of West Denpasar, East Denpasar, North Denpasar, and South Denpasar. The targeted population in this study is e-cigarette users. Meanwhile, the reachable population is the visitors to e-cigarette stores in the city of Denpasar.

The sample inclusion criteria for this study are being male, ever used an e-cigarette, and active sexually. The exclusion criteria for this study include having a congenital hypogonadism disorder, a history of surgery for severe injury to the genital organs, and being active users of conventional cigarettes within the last six months.

The minimum sample size needed is calculated with the Lemeshow formula resulting in 48 samples. Sampling will be conducted using consecutive sampling. The number of samples obtained fulfilling the inclusion criteria in this study is 51 samples. This sample will be interviewed using the ADAM score questionnaire and the sample's characteristic data questionnaire. In the analysis, the samples used are 49 samples because 2 of the samples were excluded due to they were an active conventional cigarette user.

The dependent variable in this study is hypogonadism which is determined based on the ADAM score questionnaire. The independent variable in this study is e-cigarette which is determined by the history of e-cigarette use. Active users are a person who inhales aerosols produced by e-cigarettes by at least 1 unit or 15 puffs every day in a month. The liquids used also must contain nicotine to be determined as an active user.

Research data will be perceived using the Statistical Package for the Social Sciences (SPSS®) program version 26.0 with a 95% confidence level ( $p=0,05$ ). Data analysis includes univariate analysis to determine the prevalence of hypogonadism and the e-cigarette user characteristics; and bivariate analysis to determine the association between hypogonadism and active e-cigarette use using the Pearson Chi-Square test. A result with  $p\text{-value} < 0,05$  indicates an association between hypogonadism and active e-cigarette use. In addition, a prevalence ratio (PR) test will be carried out to assess the risk of e-cigarette use against the

incidence of hypogonadism. A PR value of  $>1$  indicates an increased risk and a PR value of  $<1$  indicates a decreased risk.

### 3. Results

Data collection was conducted through the completion of questionnaires provided to the respondents. A total of 49 samples who met the inclusion and exclusion criteria became the study samples. Sample characteristics obtained such as domicile, age, marital status, BMI, and history of diseases or drug use, can be seen in Table 1.

**Table 1.** Characteristics of the Research Sample

Variable	Frequency (n=49)	Percentage (%)
<b>Domicile</b>		
Denpasar	39	79.6
West Denpasar	5	12.9
East Denpasar	6	15.4
North Denpasar	8	20.5
South Denpasar	13	33.3
Not Specific	7	17.9
Outside Denpasar	10	20.4
<b>Age (years)</b>		
19	6	12.2
20	9	18.4
21	15	30.6
22	6	12.2
23	4	8.2
24	3	6.1
25	2	4.1
26	3	6.1
31	1	2.0
Mean Age (years)	21.7	
<b>Marital Status</b>		
Marry	4	8.2
Unmarried	45	91.8
<b>BMI Classification</b>		
Very Underweight	1	2
Underweight	6	12.2
Normal	19	38.8
Overweight	6	12.2
Obesity	17	34.7
Mean BMI (kg/m2)	23 (14.9–35.9)	
<b>History of Diseases</b>	3	6.7
<b>History of Alcohol or Drug Consumption*</b>	3	6.7

\*Within the last 1 month

The history of e-cigarette smoking of the respondents is also obtained from the questionnaires provided to the respondents. Samples are distributed by total electric smoking in a month, number of smoking sessions in a day, number of puffs in one smoking session, electric smoking start history, electric smoking status, and nicotine content used. This sample distribution can be seen in Table 2.

Visitors to e-cigarette stores in Denpasar mostly are from Denpasar (79.6%). The mean age of the respondents is 21.7 years old with most of them distributed between 19-22 years old (73.4%). In this study, almost all of the respondents are unmarried (91.8%). The mean BMI of the respondents is 23 kg/m<sup>2</sup> with most of the respondents lying on the normal (38.8%) and obesity (34.7%) category. Only 3 respondents (6.7%) have a history of diseases and only 3 respondents (6.7%) have a history of alcohol or drug consumption within 1 month.

Most of the respondents smoke e-cigarettes every day (75.5%) and most of the respondents smoke e-cigarettes more than one session in a day (85.7%). Over half of the respondents (61.2%) smoke e-cigarettes at least one unit per day. Only one respondent using e-cigarette liquid contained 0% nicotine, other respondents use liquid with nicotine content varied from 0.9% to 10%. This data

combined results in 34 active e-cigarette users (69.4%) and 15 inactive e-cigarette users (30.6%).

**Table 2.** E-Smoking History of the Research Sample

Variable	Frequency (n=49)	Percentage (%)
<b>Total Electric Smoking in a Month</b>		
Every day	37	75.5
>15 days, not every day	7	14.3
<15 Days	5	10.2
<b>Number of Smoking in a Day</b>		
>1 time	42	85.7
Once	7	14.3
<b>Number of Inhalations in One Smoking</b>		
>15 <i>Puff</i>	30	61.2
(15-50 <i>Puffs</i> )	(9)	(30)
(50-100 <i>Puffs</i> )	(11)	(36.6)
(100-200 <i>Puffs</i> )	(5)	(16.7)
(200-500 <i>Puff</i> )	(5)	(16.7)
<15 <i>Puff</i>	19	38.8
<b>Start Electric Smoking</b>		
>1 year	41	83.7
<1 year	8	16.3
<b>Nicotine Content Used (%)*</b>		
0	1	2
0,9	1	2
1,4	2	4.1
2	3	6.1
3	28	57.1
5	2	4.1
6	5	10.1
8	1	2
9	1	2
10	5	10.2
<b>Electric Smoking Status</b>		
Active	34	69.4
Inactive	15	30.6

\*Consistent nicotine content used by respondents

The associations of hypogonadism with active e-cigarette uses are obtained from bivariate analysis using two-by-two tables and the Pearson Chi-Square test calculated using SPSS®. This result can be seen in Table 3. Overall, there are 13 hypogonadisms (26.5%) screened from the total of 49 samples. About 12 of the 13 hypogonadisms

(92.3%) screened in this study are an active e-cigarette user. Bivariate analysis using the Pearson Chi-Square test shows a p-value of 0.032 ( $p < 0.05$ ) and a prevalence ratio (PR) of 5.294 (CI95% 0.755-37.115). This result indicates that there is an association between the variables and there is an increased risk of hypogonadism in e-cigarette users.

**Table 3.** Bivariate Analysis of E-Cigarettes with Hypogonadism

Electric Smoking Status	Hypogonadism						p	PR	CI
	Positive		Negative		Total				
	(n)	(%)	(n)	(%)	(n)	(%)			
Active	12	35.3	22	64.7	34	100	0.032	5.294	0.755 - 37.115
Inactive	1	6.7	14	93.3	15	100			
<b>Total</b>	13	26.5	36	73.5	49	100			

#### 4. Discussion

This study involved 49 male respondents who visited e-cigarette sales places around Denpasar City. Some visitors to e-cigarette shops want to buy e-cigarette liquids and some are just starting to e-cigarettes and buy e-smoking equipment such as vapes and pods as e-smoking media.

Most of the respondents were in the age range of 19-23 years. Based on the results of interviews at several e-cigarette sales places visited, the majority of their customers are still under 25 years old. However, most respondents (83.7%) admitted to having smoked electric cigarettes for more than one year. This study found a respondent who had started smoking e-cigarettes at the age of 12 without a previous history of conventional smoking. This indicates a shift in the use of e-cigarettes, which were originally a therapeutic tool to help stop smoking habits, into a recreational tool<sup>[17]</sup>.

The BMI classification in the respondents of this study was mostly in the normal category. Only 17 respondents or around 34.7% of respondents were categorized as obese. This figure is quite high when compared to the results of Riskesdas 2018 which shows that the obesity rate in Bali is 23.3% in the Balinese population over 18 years old. This shows that there is a tendency to have a higher incidence of obesity in the Balinese population who smoke e-cigarettes. Excess weight and obesity are known to affect sperm quality and testosterone levels<sup>[18]</sup>.

A total of 6 respondents (14.3%) in this study admitted to having a history of disease or a history of consuming drugs. The history of the diseases experienced, namely asthma, tuberculosis, and vertigo is currently known to have no connection with the incidence of hypogonadism<sup>[19]</sup>. The only medication taken by the respondents and possibly related was corticosteroids taken by 2 respondents. However, studies show the impact of corticosteroid use on hypogonadism is only seen significantly after long-term consumption<sup>[20]</sup>.

The majority of respondents (75.5%) admitted to smoking electric cigarettes every day. A total of 7 respondents (14.3%) smoked electric smoke more than 15 days a month and another 5 respondents (10.2%) smoked electric smoke less than 15 days a month. There were 3 respondents (6.1%) who smoked electric every day but did not reach 1 unit or 15 *Puff* every day so it cannot be categorized as active smoking. 1 unit or 15 *puffs* was determined by equalizing the levels of substances contained in e-cigarette aerosols with smoke from conventional cigarettes<sup>[21]</sup>. Another twelve respondents (24.5%) who do not smoke an electric cigarette every day are

also categorized as inactive e-smokers. This is to ensure consistent exposure to e-cigarettes.

The nicotine content in the e-cigarette liquid used by respondents varied from 0% to 10%. The most commonly used nicotine content by respondents was 3%. On the liquid packaging, it is usually written 30 mg of nicotine for a content of 3% in 30 ml of liquid. The nicotine content contained in conventional cigarettes is generally around 1.19 mg so the nicotine content contained in 1 ml of e-cigarette liquid with a content of 3% is approximately equivalent to 1 conventional cigarette<sup>[22]</sup>. Based on this comparison, if the research is conducted on the same subject, the results of the study on conventional cigarette users can give similar results to e-cigarette users. It has previously been known that nicotine exposure can affect blood testosterone levels associated with the incidence of hypogonadism<sup>[23]</sup>.

Cases of hypogonadism assessed using the ADAM score questionnaire in this study were quite high, which was around 26.5%. This result is very high because based on previous research by Liu *et al.*, the prevalence of hypogonadism in adulthood in China is only about 7.8% which continues to increase with age (Liu *et al.*, 2021). One of the things that affects this result is that the positive assessment of hypogonadism in this study is assessed using only the ADAM score questionnaire which is a screening for hypogonadism<sup>[25]</sup>.

Hypogonadism is a disease syndrome caused by a decrease in testosterone levels to a certain extent. Hypogonadism can be divided into two types, namely primary hypogonadism associated with the hypothalamus and pituitary gland, while secondary hypogonadism is associated with damage to the gonadal glands or testicles<sup>[26]</sup>. In this study, the types of hypogonadism that are studied concerning the use of e-cigarettes are *Late Onset Hypogonadism* (LOH) or hypogonadism that only occurs in adulthood<sup>[27]</sup>.

One of the risk factors for secondary hypogonadism is smoking habits (Peng *et al.*, 2021). Cigarette smoke contains harmful substances, such as nicotine, formaldehyde, lead, and other micrometals<sup>[21]</sup>. Some of these ingredients are also found in aerosols produced by e-cigarettes even at lower concentrations<sup>[29]</sup>. This adds to the estimated relationship between e-cigarette use and the incidence of hypogonadism in adult men. One conventional cigarette is considered equivalent to one unit or 15 *Puff* from the use of e-cigarettes based on the content of substances contained in them<sup>[30]</sup>.

A statistical test in the form of the Pearson Chi-Square test conducted in this study obtained a p-value of 0.032 ( $p < 0.05$ ) which means that there is a meaningful relationship between the use of e-



cigarettes and the incidence of hypogonadism in adult men. From these results, it can be concluded that the H0 or null hypothesis was rejected and the H1 or alternative hypothesis was accepted, which means that there is a positive relationship between e-cigarette use and hypogonadism in adult men<sup>[31]</sup>.

At the moment, research linking e-cigarettes to the hormone testosterone is still very limited. There is a study that shows that there is a possible relationship between e-cigarette use and the incidence of erectile dysfunction in men due to endothelial damage<sup>[32]</sup>. In addition, there was another study on test animals in the form of Wistar rats that showed a decrease in testicular volume in exposure to e-cigarette aerosols. This is one of them related to the decrease in testosterone levels<sup>[33]</sup>.

The highly positive hypogonadism screening results indicate the need for further research that examines testosterone levels in e-cigarette users when compared to those who do not e-cigarettes to prove the results of this study. This is due to the high level of sensitivity, but the low level of specificity of the ADAM score questionnaire used in this study so further tests are needed to confirm the diagnosis of hypogonadism<sup>[34]</sup>.

The account *prevalence ratio* (PR) was obtained as a figure of 5.294 (CI95% 0.755-37,115). This figure shows an increased risk of 5.294 times experiencing hypogonadism in a person who smokes e-cigarettes. However, the results *Confidence Interval* The wide CI indicates the instability of the information so the statistical strength for drawing risk conclusions in this study is still weak. Follow-up research with a larger sample size needs to be done to obtain a narrower CI so that it can produce more accurate research conclusions<sup>[35]</sup>.

The content of harmful substances in conventional cigarettes is quite similar to e-cigarettes so comparisons can be made to estimate the risk to e-cigarette users. Research conducted by Jang *et al.* shows a significant relationship between smoking habits and late-onset hypogonadism<sup>[36]</sup>. Similar research was conducted by Salam *et al.*, in Egypt showed a statistically significant decrease in serum testosterone levels of a person who had a smoking habit<sup>[37]</sup>.

The causes of secondary hypogonadism in adult men are multifactorial so they can be caused by many things. Some of the risk factors associated with hypogonadism in adulthood are smoking habits, obesity, diabetes, drug consumption, HIV/AIDS, and infections<sup>[38],[39]</sup>. Hypogonadism is more common and occurs more often after the age of 40<sup>[40]</sup>. However, in this study which involved screening for hypogonadism using an ADAM score questionnaire a person who smoked e-cigarettes had

an average age of 21.7 years. These results still need to be further researched to be able to establish the relationship between e-cigarette use and the incidence of hypogonadism because the type of questionnaire used in this study is still screening<sup>[41]</sup>.

The questions contained in the ADAM score questionnaire may cause bias in this study because some questions may not be related to hypogonadism at all. Some of these questions, such as decreased enthusiasm for life, often feeling sad or angry, feeling too lazy to exercise, and quickly drowsy after dinner. Some of these things can be related to respondents' lifestyles, such as sedentary lifestyles, and emotional states, such as job stress<sup>[40],[41]</sup>. In addition, there are very subjective questions, such as often feeling weak, decreased physical strength, and decreased ability to work. Some of these things can be related to the lack of exercise habits and the high workload that respondents are experiencing<sup>[42],[43]</sup>. These two problems are very relevant because the population of respondents in this study is in the age range that has not yet entered the age of risk of hypogonadism<sup>[44]</sup>.

The use of conventional cigarettes has previously been classified as a risk factor for hypogonadism and e-cigarettes emit harmful components similar to conventional cigarettes, so this study is expected to increase the awareness regarding the dangers of e-cigarettes to the incidence of hypogonadism<sup>[45]</sup>. This research is one of the latest studies that discusses the dangers of e-cigarettes. This research is expected to be a driving force for future studies that discuss the dangers of e-cigarettes to health.

## 5. Conclusion

Based on this study conducted on the visitors of e-cigarette stores in the city of Denpasar, there is a meaningful relationship between active e-cigarette use and hypogonadism in adult men marked by a p-value of 0.032 ( $p < 0.05$ ). The results of hypogonadism screening conducted in the city of Denpasar in this study showed a high prevalence, which was around 26.5%. Among the group of active e-cigarette users, this number is even higher reaching 35.3% of the total active e-cigarette smokers included in this sample. Based on the prevalence ratio, there is a 5.294 times increased risk of hypogonadism among active e-cigarette users.

On conducting this study, there are some limitations encountered in this study. There is a need for a larger sample size to increase the statistical strength of the research data. This is necessary to be able to obtain a stronger conclusion about the association between hypogonadism and active e-cigarette use.

Community-based research may need to be done to be able to obtain respondents with an age group over 30 years old. The use of random sampling such as random cluster sampling may need to be done to minimize the potential bias in this research.

### Author's Contribution

All authors have contributed to the final manuscript.

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### Conflict of Interest

The authors declare no conflict of interest.

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### References

1. Widiyanti NK, Kurniasari NMD, Trapika IGMGSC, Astuti PAS. Vape Store Density and Proximity to Schools in Denpasar, Bali, Indonesia. *Tob Control* [Internet]. 2023 Aug 4;tc-2023-058037. Available from: <http://tobaccocontrol.bmj.com/content/early/2023/08/04/tc-2023-058037.abstract>
2. Anonym. Global Adult Tobacco Survey Fact Sheet Indonesia 2021 Gats Objectives. World Heal Organ. 2021.
3. Anonym. WHO. Tobacco: E-cigarettes [Internet]. 2021. Available from: <https://www.who.int/news-room/questions-and-answers/item/tobacco-e-cigarettes>
4. Szumilas K, Szumilas P, Grzywacz A, Wilk A. The Effects of E-cigarette Vapor Components on The Morphology and Function of The Male and Female Reproductive Systems: A Systematic Review. *Int J Environ Res Public Health*. 2020;17(17):1–13.
5. Overbeek DL, Kass AP, Chiel LE, Boyer EW, Casey AMH. A Review of Toxic Effects of Electronic Cigarettes/vaping in Adolescents and Young Adults. *Crit Rev Toxicol* [Internet]. 2020;50(6):531–8. Available from: <https://doi.org/10.1080/10408444.2020.1794443>
6. Palmisani J, Abenavoli C, Famele M, Di Gilio A, Palmieri L, de Gennaro G, et al. Chemical characterization of electronic cigarette (e-cigs) refill liquids prior to EU tobacco product directive adoption: Evaluation of BTEX contamination by HS-SPME-GC-MS and identification of flavoring additives by GC-MS-O. *Atmosphere (Basel)*. 2020;11(4):1–21.
7. Duca Y, Aversa A, Condorelli RA, Calogero AE, Vignera S La. Substance Abuse and Male Hypogonadism. *J Clin Med*. 2019;8(732):1–26.
8. Price LR, Martinez J. Cardiovascular, carcinogenic and reproductive effects of nicotine exposure: A narrative review of the scientific literature. *F1000Research* [Internet]. 2020 Jan 9;8(1586):1–34. Available from: <https://doi.org/10.12688/f1000research.20062.2>
9. Eaglin AR. Male and Female Hypogonadism. *Nurs Clin North Am* [Internet]. 2018 Sep;53(3):395–405. Available from: <https://doi.org/10.1016/j.cnur.2018.04.006>
10. Salonia A, Rastrelli G, Hackett G, Seminara SB, Huhtaniemi IT, Rey RA, et al. Paediatric and Adult-Onset Male Hypogonadism. *Nat Rev Dis Prim* [Internet]. 2019 Dec 30;5(1):38. Available from: <http://www.nature.com/articles/s41572-019-0087-y>
11. Giagulli VA, Castellana M, Lisco G, Triggiani V. Critical Evaluation of Different Available Guidelines for Late-Onset Hypogonadism. *Andrology* [Internet]. 2020 Nov 12;8(6):1628–41. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/andr.12850>
12. Jaschke N, Wang A, Hofbauer LC, Rauner M, Rachner TD. Late-Onset Hypogonadism: Clinical Evidence, Biological Aspects and Evolutionary Considerations. *Ageing Res Rev*. 2021 May;67:101301.
13. Allen MS, Tostes RC. Cigarette Smoking and Erectile Dysfunction: An Updated Review with a Focus on Pathophysiology,

- E-cigarettes, and Smoking Cessation. *Sex Med Rev*. 2023;11(1):61–73.
14. Monageng E, Offor U, Takalani NB, Mohlala K, Opuwari CS. A Review on the Impact of Oxidative Stress and Medicinal Plants on Leydig Cells. *Antioxidants*. 2023;12(8):1559.
15. Vivarelli F, Canistro D, Cirillo S, Cardenia V, Rodriguez-Estrada MT, Paolini M. Impairment of Testicular Function in Electronic Cigarette (e-cig, e-cigs) Exposed Rats Under Low-Voltage and Nicotine-Free Conditions. *Life Sci [Internet]*. 2019 Jul;228:53–65. Available from: <https://www.sciencedirect.com/science/article/pii/S0024320519303273>
16. Szeliga A, Kunicki M, Maciejewska-Jeske M, Rzewuska N, Kostrzak A, Meczekalski B, et al. The Genetic Backdrop of Hypogonadotropic Hypogonadism. *Int J Mol Sci*. 2021;22(24):1–12.
17. Breland A, Soule E, Lopez A, El-hellani A, Eissenberg T. Electronic Cigarettes: What Are They and What Do They Do? *Ann N Y Acad Sci*. 2018;1394(1):5–30.
18. Wittert G, Grossmann M. Obesity, Type 2 Diabetes, and Testosterone in Ageing Men. *Rev Endocr Metab Disord*. 2022;23(6):1233–42.
19. Marcelli M, Mediawala SN. Male Hypogonadism: A Review. *J Investig Med*. 2020;68(2):335–56.
20. Mohammed AG, Mansour AA, Ahmed JH. Effect of Exogenous Glucocorticoids on Male Hypogonadism. *Biomed Reports*. 2020;13(3):1–8.
21. Münzel T, Hahad O, Kuntic M, Keaney JF, Deanfield JE, Daiber A. Effects of tobacco cigarettes, e-cigarettes, and waterpipe smoking on endothelial function and clinical outcomes. *Eur Heart J [Internet]*. 2020 Nov 1;41(41):4057–70. Available from: <https://pubmed.ncbi.nlm.nih.gov/32585699>
22. Soleimani F, Dobaradaran S, De-la-Torre GE, Schmidt TC, Saeedi R. Content of Toxic Components of Cigarette, Cigarette Smoke vs Cigarette Butts: A Comprehensive Systematic Review. *Sci Total Environ*. 2022;813.
23. Gryzinski GM, Bernie HL. Testosterone Deficiency and The Aging Male. *Int J Impot Res*. 2022;34(7):630–4.
24. Liu YJ, Shen XB, Yu N, Shang XJ, Gu YQ, Zuo LD, et al. Prevalence of Late-onset Hypogonadism Among Middle-Aged and Elderly Males in China: Results from A National Survey. *Asian J Androl*. 2021;23(2):170–7.
25. Farahani MA, Khachian A, Vakilian P, Mahmoudi M. Androgen Deficiency in Aging Males: Translation and Validation Study of the Iranian Version. *Iran J Nurs Midwifery Res*. 2021;26(2):144–9.
26. Zuniga RE, Rogol AD. Functional Hypogonadism in Adolescence: An Overlooked Cause of Secondary Hypogonadism. *Endocr Connect*. 2023;12(11).
27. Giagulli VA, Castellana M, Lisco G, Triggiani V. Critical Evaluation of Different Available Guidelines for Late-onset Hypogonadism. *Andrology*. 2020;8(6):1628–41.
28. Liu Q, Peng X, Gu Y, Shang X, Zhou Y, Zhang H, et al. Associations Between Smoking, Sex Hormone Levels and Late-Onset Hypogonadism in Men Differ Depending on Age. *Aging (Albany NY)*. 2021 Feb;13(4):5226–37.
29. Margham J, McAdam K, Cunningham A, Porter A, Fiebelkorn S, Mariner D, et al. The Chemical Complexity of e-Cigarette Aerosols Compared with the Smoke From a Tobacco Burning Cigarette. *Front Chem*. 2021;9(September):1–16.
30. Sapru S, Vardhan M, Li Q, Guo Y, Li X, Saxena D. E-cigarettes use in the United States: reasons for use, perceptions, and effects on health. *BMC Public Health [Internet]*. 2020 Dec 9;20(1):1518. Available from: <https://doi.org/10.1186/s12889-020-09572-x>
31. Shen C, Panda S, Vogelstein JT. The Chi-Square Test of Distance Correlation. *J Comput Graph Stat a Jt Publ Am Stat Assoc Inst Math Stat Interface Found North Am*. 2022;31(1):254–62.
32. Pincus J, Sandoval V, Dick B, Sanekommu G, Rajasekaran R, Ramasamy R, et al. E-Cigarette-Associated Endothelial Damage: A Potential Mechanism for Erectile Dysfunction. *Sex Med Rev [Internet]*. 2022 Jan 1;10(1):168–73. Available from: <https://doi.org/10.1016/j.sxmr.2021.01.003>
33. Silitonga HTH, Rambung E, Sekarputri CH, Nugraheni ES, Mellyanawati M. The Impact of Conventional Cigarettes, Nicotine-containing and Nicotine-free Electric Cigarettes on Testicular Weight of Male Wistar Rats. *Bul Poltanesa [Internet]*. 2024 Jun 19;25(1):140–6. Available from: <https://e->



- journal.politanisamarinda.ac.id/index.php/t  
anesa/article/view/3042
34. Lestari AAADI, Pramesemara IGN, Kurniawan Y. Relationship Between Waist Circumference and The Event of Andropause in Male Employees in Government Institutions of Badung Regency. *Indones Androl Biomed J*. 2021;2:9–15.
35. Kamper SJ. Showing Confidence (Intervals). *Brazilian J Phys Ther* [Internet]. 2019;23(4):277–8. Available from: <https://doi.org/10.1016/j.bjpt.2019.01.003>
36. Jang SS, Cho YJ, Moon H, Kim HJ, Lee GH, Kim YA. Association between Smoking and Symptoms of Late-Onset Hypogonadism in Korean Men. *Korean J Fam Pract*. 2024;14(1):11–8.
37. Salam MAA El, Zaki S, Mousa MS, Motawi A. Effect of Cigarette Smoking on Serum Testosterone Level Among Male Smokers. *Egypt J Chest Dis Tuberc*. 2021;70(1):124–7.
38. Ross A, Bhasin S. Hypogonadism: Its Prevalence and Diagnosis. *Urol Clin North Am*. 2016 May;43(2):163–76.
39. Spaziani M, Carlomagno F, Tarantino C, Angelini F, Vincenzi L, Gianfrilli D. New Perspectives in Functional Hypogonadotropic Hypogonadism: Beyond Late Onset Hypogonadism. *Front Endocrinol (Lausanne)*. 2023;14:1184530.
40. Park JH, Moon JH, Kim HJ, Kong MH, Oh YH. Sedentary Lifestyle: Overview of Updated Evidence of Potential Health Risks. *Korean J Fam Med*. 2020;41(6):365.
41. Connor DBO, Thayer JF, Vedhara K. Stress and Health: A Review of Psychobiological Processes. *Annu Rev Psychol*. 2021;72(1):663–88.
42. Ludyga S, Gerber M, Pühse U, Looser VN, Kamijo K. Systematic Review and Meta-Analysis Investigating Moderators of Long-Term Effects of Exercise on Cognition in Healthy Individuals. *Nat Hum Behav*. 2020;4(6):603–12.
43. Grasdalsmoen M, Eriksen HR, Lønning KJ, Sivertsen B. Physical Exercise, Mental Health Problems, and Suicide Attempts in University Students. *BMC Psychiatry*. 2020;20:1–11.
44. Huhtaniemi IT, Wu FCW. Ageing Male (Part I): Pathophysiology and Diagnosis of Functional Hypogonadism. *Best Pract Res Clin Endocrinol Metab* [Internet]. 2022;36(4):101622. Available from: <https://www.sciencedirect.com/science/article/pii/S1521690X22000094>
45. Parameswari R, Sridharan TB. Cigarette Smoking and Its Toxicological Overview on Human Male Fertility—A Prospective Review. *Toxin Rev* [Internet]. 2021;40(2):145–61. Available from: <https://doi.org/10.1080/15569543.2019.1579229>.