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# Impact of Contemporary Low Dose Aspirin Use and Cardiovascular Disease

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## Introduction

**Cardiovascular disease (CVD)** is the leading cause of death in the U.S. and worldwide claiming **17.9 million deaths, representing 31% of all global deaths** [1]

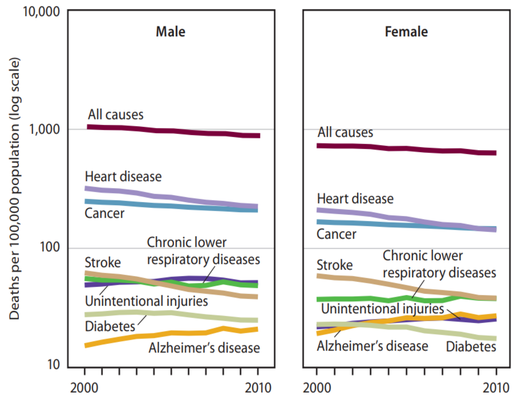


**Figure:1** Source: CDC/NCHS, Health, United States, 2013, Table 20. Data from the National Vital Statistics System (NVSS).

- Aspirin is a widely prescribed antiplatelet medicine for the treatment and prevention of CVD. It is estimated that **48.7 million US adults** are taking aspirin for prevention of cardiovascular disease (CVD). The majority (~73%) for primary prevention [2].
- The literature supports the role of low dose of aspirin in the primary prevention of CVD**, recent studies have shown this topic to be controversial**. Evidences unveil discrepancies between clinical guidelines for the use of low aspirin dosage towards primary prevention of CVD and the clinical pattern followed by patients [3.4].

## Objective

Using a nationally representative sample, this study sought to examine impact of **low dose of aspirin and coronary artery disease** in order to assess a plausible association between aspirin and a CAD.

## Methods and Materials

**Sample: NHANES 2013-2014, N=62,776**
**Data items:** Age, Male, BMI, Smoking, Alcohol use, Admission to hospital, cardiovascular diseases, Comorbidities

**Statistical analyses:**
1) descriptive statistics, including bivariate analysis used to identify differences between the groups, and test the association between Aspirin and Cardiovascular diseases, and between Aspirin and each of the confounding variables: Age, Male, BMI, Smoking, Alcohol use, Admission to hospital and other Comorbidities
2) a multivariate regression was used to test the relationship between aspirin and cardiovascular disease while controlling for Age, Male, BMI, Smoking, Alcohol use, Admission to hospital and other Comorbidities

## Results

**Table 1. Descriptive Statistics**

| *Variables* | *Total* | *Low dose of aspirin* *Yes* N=4829 | *No* N=9757 | $\chi^2$ / *T test* | p |
|---|---|---|---|---|---|
| ***Age** (Mean/ Standard deviation)* | N=62,776 | 64.47 (10.54) | 54.64 (10.90) | 51.828 | 0.112 |
| ***Age*** (%) | | | | 2280.938 | <0.001 |
| *40-49* | 29.1 | 8.8 | 39.1 | | |
| *50-59* | 28.8 | 23.8 | 31.3 | | |
| *60-69* | 22.7 | 32.9 | 17.7 | | |
| *More than 70* | 19.3 | 34.6 | 11.8 | | |
| ***Male*** (%) | 47.3 | 51.4 | 45.2 | 49.813 | <0.001 |
| ***BMI (Kg/m2)*** (%) | | | | 102.144 | <0.001 |
| ≤25 | 26 | 20.8 | 28.6 | | |
| *25.1-40* | 66.6 | 71.1 | 64.4 | | |
| *40.1* ≥ | 7.4 | 8.1 | 7.0 | | |
| ***Smoking*** (%) | 46.7 | 52.8 | 43.7 | 107.687 | <0.001 |
| ***Alcohol use*** (%) | 77 | 75.2 | 77.9 | 12.501 | <0.001 |
| ***Admission to hospital*** (%) | | | | 426.352 | <0.001 |
| *0-2 times* | 57 | 45 | 63 | | |
| *3-5 times* | 29.1 | 37.3 | 25.1 | | |
| *≥6 times* | 13.9 | 17.7 | 12 | | |
| ***ASA indication*** (%) | | | | | |
| *Myocardial Infarction* | 5.1 | 11.9 | 1.7 | 692.463 | <0.001 |
| *Angina Pactoris* | 3.1 | 7.5 | 1 | 443.088 | <0.001 |
| *Coronary Artery Disease* | 5.5 | 13.7 | 1.4 | 947.124 | <0.001 |
| *Congestive Heart Failure* | 3.9 | 7.8 | 1.9 | 299.552 | <0.001 |
| *Stroke* | 4.4 | 8.9 | 2.2 | 345.786 | <0.001 |
| ***Comorbidities*** (%) | | | | | |
| *High blood pressure* | 46.5 | 64.7 | 37.6 | 952.229 | <0.001 |
| *Hyperlipidemia* | 47.9 | 67.5 | 38.2 | 1102.180 | <0.001 |
| *Diabetes* | 14.7 | 26.3 | 9 | 828.370 | <0.001 |
| *cancer* | 15.8 | 24.5 | 11.5 | 408.191 | <0.001 |
| *Asthma* | 14.1 | 16.3 | 13.0 | 29.213 | <0.001 |
| *Arthritis* | 38.2 | 50.4 | 32.1 | 454.201 | <0.001 |
| *COPD* | 5.1 | 10.5 | 2.4 | 441.200 | <0.001 |

**Table 2. Multivariable Logistic Regression**

| Variables | OR | Lower | Upper | p |
|---|---|---|---|---|
| **Unadjusted Model** | | | | |
| Daily low-dose aspirin | 11.731 | 9.593 | 14.347 | .000 |
| Constant | .537 | | | .000 |
| **Adjusted Model** | | | | |
| Daily low-dose aspirin | 3.201 | 2.522 | 4.062 | .000 |
| AGE (40-49) REF | | | | .000 |
| AGE(50-59) | .294 | .173 | .502 | .000 |
| AGE(60-69) | .150 | .090 | .252 | .000 |
| AGE (70+) | .109 | .065 | .183 | .006 |
| Male | .607 | .490 | .750 | .000 |
| BMI ≤25 | | | | .627 |
| BMI 25.1-40 | .946 | .740 | 1.210 | .695 |
| BMI 40.1+ | 1.141 | .730 | 1.785 | .562 |
| Smoked 100+ cigarettes lifetime | 1.350 | 1.091 | 1.671 | .006 |
| Had at least 12 alcohol drinks/1yr | .893 | .701 | 1.137 | .358 |
| Hospital (6+ times) REF | | | | .000 |
| Hospital (0-2 times) | 1.733 | 1.314 | 2.285 | .000 |
| Hospital (3-5 times) | 1.441 | 1.103 | 1.884 | .007 |
| Congestive heart failure | 2.931 | 2.164 | 3.970 | .000 |
| Angina/angina pectoris | 13.361 | 9.942 | 17.956 | .000 |
| Heart attack | 8.223 | 6.481 | 10.433 | .000 |
| Stroke | 1.043 | .750 | 1.449 | .802 |
| High blood pressure | 1.682 | 1.347 | 2.099 | .000 |
| High cholesterol level | 1.251 | 1.001 | 1.564 | .049 |
| Doctor told you have diabetes | 1.043 | .859 | 1.266 | .671 |
| Cancer or malignancy | .782 | .615 | .995 | .046 |
| Asthma | .735 | .543 | .994 | .046 |
| Arthritis | .760 | .613 | .943 | .013 |
| COPD | 1.981 | 1.458 | 2.693 | .000 |
| Constant | .000 | | | .000 |

**Descriptive Statistics:**
- Among 62,776 participants (40 years or old), 4829 (7.7%) were taking low dose of aspirin (mean age = 64.47 ± 10.54 years).
- Male have higher proportion in low dose of aspirin usage (51.4%) than female. There were an increase in usage of ASA in more than 70 years of age group (34.6%), compare to other age groups.
- People with 25.1-40 KG/M2 of BMI (71.1%), smoker (52.8%) , alcoholic (75.2%) with hospital admission for at least 0-2 times (45%) have higher portion in ASA use.
- More than half of people, who were using ASA had **high blood pressure (64.7%)** and **hyperlipidemia (67.5%).** Almost half people seem to have **arthritis (50.4%)** as comorbidity. There were also some other comorbidities associated with ASA usage, like **diabetes (26.3%)**, diagnosis of cancer (24.5%), asthma (16.3) and COPD (10.5%).
- A crosstabulation analysis carried out to test association between low dose of aspirin and coronary artery disease. **A significant association found between $\chi^2$ (1) = 692.463, p<.001, which suggest significant association between low dose of aspirin usage and coronary artery disease.**

**Logistic Regression:**

**Unadjusted model ($\chi^2$ (1) =829.375, p <.001):**
Unadjusted model explained 17.6% (Nagelkerke $R^2$) of the variation of having coronary artery disease, and correctly classified 94.5% of cases. People who take low dose of aspirin are 11.7 times more likely to have had coronary artery disease than those who don't.

**Adjusted model ($\chi^2$ (15) =2422.801, p <.001):**
- Adjusted model explained 48.4% (Nagelkereke $R^2$) of the variation, and correctly classified 96.1% of cases.
- Those prescribed low dose aspirin are more likely to have CAD than patients who are not. As age increases among those prescribed aspirin, the odds of having CAD deceases.
- BMI and alcohol use exhibit no significant association with CAD. In contrast, those who have smoked at least 100 cigarettes in life are 1.3 times more likely to have CAD than those who have not.
- Patients who were hospitalized had higher odds of having CAD than non-hospitalized patients. Among those hospitalized, patients hospitalized 0-2 times had a higher odds of having CAD than those who were hospitalized 3 or more times.
- Congestive heart failure, angina pectoris, myocardial infarction, and COPD have a significant positive association with CAD. These patients have a higher odds of having CAD than patients without these diseases. Stroke diagnosis has no significant association with CAD.
- Patients with high cholesterol and high blood pressure have a higher odds of having CAD than patients who do not. Diagnoses of diabetes and COPD also increase the odds of CAD
- Patients with asthma and arthritis have a lower odds of having CAD than patients without these comorbidities.

## Conclusions

- Primary and secondary prevention of CAD is reflected in the data showing an inverse correlation between age and CAD among those prescribed low dose aspirin. The youngest age group (40-49 years) may have the highest odds due to lower primary prevention of CAD in this age group. It suggests that low dose aspirin is used in response to existing CAD rather than as a primary prevention technique. Above 50 years, low dose aspirin is routinely used in primary prevention regardless of existing CAD.
- The non significant association between BMI and CAD is explained by the fact that BMI quantifies general adiposity. It can not give an accurate view regarding fat distribution in body. While fat distribution is an important determinant of CAD, BMI shouldn't be use a reliable indictor of CAD. Central obesity is important predictor for CAD prevalence, which can be measured using waist circumference. The American Heart Association (AHA) and National Heart, Lung, and Blood Institute (NHLBI) set the thresholds at ≥ 102 cm in men and ≥88 cm in women [6]
- The association between smoking and CAD occurs because smoking initiates atherogenesis through oxidation and endothelial scarring. In turn, subsequent endothelial dysfunction increases susceptibility of healthy vessels for atheroma formation. Smoking also increases the formation of proatherogenic lipids and increases blood pressure [7]
- The decrease in high-density lipoproteins (HDL), and the accumulation of proatherogenic lipids like triglycerides (TGs), trans fatty acids (Tans FA), and low density lipoproteins (LDL) will speed up atherogenesis. Induced inflammation, oxidation, and lipoperoxidation may differ depending on the severity of vascular scarring. Measuring these factors may help improve assessment when determining atherosclerosis progression. Specifically, measuring Trans FA accumulation maybe be a predictive factor of con-current disease among CAD patients [8].
- Patients with COPD have a prominent systemic inflammatory response due to hyperactive immune systems., hence the positive association. C-reactive protein (CRP), is a known marker of systemic inflammation increases in stable and exacerbated conditions of COPD. These instigate a noxious environment for vessel integrity. studies confirm the role of CRP in CAD progression [9].

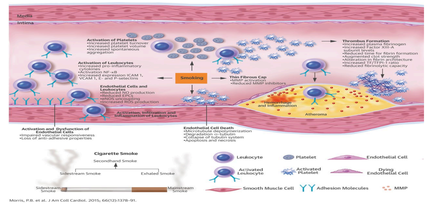


**Figure:2.** *Cardiovascular Effects of Exposure to Cigarette Smoke and Electronic Cigarettes.* [5]

**Study Limitations**
- The data is representative of the U.S population across demographics and co-morbidities (e.g. CVD, DM, HTN, Asthma, Cancer, COPD). The data then has external validity.
- Since the study is cross-sectional, the data shows no causal association between CAD and low dose aspirin use. Only correlational data has been extrapolated. Additionally, aspirin use may have been misclassified, as some patients may have used OTC aspirin instead of the prescribed dose.
- Stratifying the data by additional factors such as race, lifestyle, PVD and Rheumatic heart disease will increase the strength of the study

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