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## 1. LITERATURE REVIEW ON IQOS USE AND DISEASE RISK

### 1.1. Results

The literature review identified 4 studies assessing the association between THS use and risk of smoking-related diseases[1-4]. Three out of the four studies [1, 2, 4] were part of the 2022 Annual Report submitted to the US FDA. The fourth study [3] will be submitted to the US FDA in the 2023 Annual Report.

#### 1.1.1. CVD Risk

Two relevant studies assessing CVD risk were identified – one from South Korea [1] and the other from Japan [2]. The study from Japan employed a cross-sectional design and the one from South Korea used a cohort design. Evidence from the study from Japan was classified as moderate and that of the South Korean study was classified as strong.

In a cross-sectional study, Zaitzu et al [2] assessed the association between ever THS use and history of hypertensive disorders in pregnancy (e.g., pre-eclampsia) among 558 women. Compared to never THS users, ever users tended to have a higher risk of hypertensive disorders, but the association was not statistically significant (odds ratio [OR]=2.78, 95% confidence interval [95%CI]: 0.84-9.15).

In a very large cohort study, Choi et al [1] investigated the association of changes in noncombustible nicotine or tobacco product (NNTP: THS and electronic cigarettes) and CC habits with CVD risk among about 5.2 million men aged 20+ years. Incident CVD was defined as hospitalization for coronary heart disease (CHD) or stroke for 2+ days. Participants were followed over a period of 2 years. Compared to exclusive CC smoking, recent (<5 years) CC quitting without NNTP use (hazard ratio [HR]=0.81, 95%CI: 0.78-0.84), recent (<5 years) CC quitting with NNTP use (HR=0.77, 95%CI: 0.65-0.91), long-term (≥5 years) CC quitting without NNTP use (HR=0.63, 95%CI: 0.61-0.65), long-term (≥5 years) CC quitting with NNTP use (HR=0.77, 95%CI: 0.58-1.00), and dual use of CC and NNTP (HR=0.83, 95%CI: 0.79-88) were associated with reduced CVD risk after adjusting for relevant confounding factors. Recent (<5 years) CC quitters with (vs without) NNTP use (HR=1.31, 95%CI: 1.01-1.70) and long-term (≥5 years) CC quitters with (vs without) NNTP use (HR=1.70, 95%CI: 1.07-2.72) had increased risk of CVD. The authors conducted additional analysis specifically for CHD as the outcome of interest. Compared to exclusive CC smokers, recent CC quitters without NNTP use (HR=0.86, 95%CI: 0.82-0.90), recent CC quitters with NNTP use (HR=0.83, 95%CI: 0.67-1.03), long-term CC quitters without NNTP use (HR=0.69, 95%CI: 0.67-0.72), long-term CC quitters with NNTP use (HR=0.94, 95%CI: 0.67-1.31), dual users of CC and NNTP (HR=0.89, 95%CI: 0.83-0.96) still had lower risk of CHD, but the association for recent CC quitters with NNTP use and long-term CC quitters with NNTP use lost statistical significance.

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### 1.1.2. Risk of Stroke

The literature review on THS use and risk of stroke identified one relevant cohort study based on about 5.2 million men aged 20+ years in South Korea [1]. Incident stroke was defined as hospitalization for stroke for 2+ days, and evidence from the study was classified as strong. Compared to exclusive CC smoking, recent (<5 years) CC quitting without NNTP use (HR=0.76, 95%CI: 0.72-0.80), recent (<5 years) CC quitting with NNTP use (HR=0.71, 95%CI: 0.54-0.91), long-term (≥5 years) CC quitting without NNTP use (HR=0.57, 95%CI: 0.55-0.59), long-term (≥5 years) CC quitting with NNTP use (HR=0.57, 95%CI: 0.36-0.91), and dual use of CC and NNTP (HR=0.76, 95%CI: 0.70-0.83) were associated with reduced risk of stroke after adjusting for relevant factors. No significant difference in risk of stroke was found between recent CC quitting with (vs without) NNTP use (HR=0.93, 95%CI: 0.72-1.21) or long-term CC quitting with (vs without) NNTP use (HR=1.01, 95%CI: 0.63-1.60).

### 1.1.3. Risk of Respiratory Diseases

Two relevant cohort studies were identified – one from South Korea [1] and the other from Italy [4]. The sample size ranged from 38 [4] to about 5.2 million participants [4]. Evidence from both studies was classified as strong.

Choi et al [1] investigated the association of changes in NNTP and CC habits with COPD risk. Incident COPD was assessed from hospital records. Compared to exclusive CC smoking, recent (<5 years) CC quitting without NNTP use (HR=0.90, 95%CI: 0.86-0.94), long-term (≥5 years) CC quitting without NNTP use (HR=0.51, 95%CI: 0.49-0.52), and dual use of CC and NNTP (HR=0.81, 95%CI: 0.74-0.88) were associated with reduced COPD risk after adjusting for relevant factors. Recent CC quitters with NNTP use also had 22% lower risk of COPD as compared to exclusive CC smokers (HR=0.78, 95%CI: 0.54-1.13), but the association was not statistically significant. The risk of COPD was comparable between long-term CC quitters with NNTP use and exclusive CC smokers (HR=1.03, 95%CI: 0.83-1.28). Additionally, long-term CC quitters with (vs without) NNTP use had increased risk of COPD (HR=1.55, 95%CI: 1.07-2.24).

Polosa et al [4] compared COPD progression between THS users and CC smokers. Participants with COPD were followed over a period of 3 years. Results showed no significant changes in FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC ratio during the study period in both CC smokers and THS users. However, while mean COPD assessment test score increased by 5% in CC smokers (from 19.0 to 20.0), it decreased by 25% in THS users during the 3-year study period (from 20.0 to 15.0). Additionally, there was a substantial decrease in annual exacerbations by about 38% in THS users (from 2.1 to 1.3), whereas only a 5% decrease was observed in CC smokers (from 2.2 to 2.1). Moreover, the mean 6-minute walking distance increased in both CC smokers and THS users, but the difference was larger for THS users (25% vs 8%).

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#### 1.1.4. Risk of Cancer

One relevant cohort study was identified. Choi et al [1] investigated the association of changes in NNTP and CC habits with lung cancer risk among about 5.2 million men aged 20+ years in South Korea. Participants were followed over a period of 2 years, and incident lung cancer was assessed from hospital records.

Compared to exclusive CC smoking, long-term ( $\geq 5$  years) CC quitting without NNTP use (HR=0.54, 95%CI: 0.51-0.57), and dual use of CC and NNTP (HR=0.76, 95%CI: 0.64-0.90) were associated with reduced COPD risk after adjusting for relevant factors. No significant difference in lung cancer risk was observed in long-term CC quitters with NNTP use (HR=0.98, 95%CI: 0.53-1.82). The risk of lung cancer was slightly elevated in recent ( $< 5$  years) CC quitters without NNTP use (HR=1.09, 95%CI: 1.01-1.18) and recent ( $< 5$  years) CC quitters with NNTP use (HR=1.42, 95%CI: 0.99-2.02) as compared to exclusive CC smokers. Additionally, long-term CC quitters with (vs without) NNTP use had 81% increased risk of lung cancer (HR=1.81, 95%CI: 0.97-3.37), but the association did not reach statistical significance.

#### 1.1.5. Risk of Diabetes

The literature review on THS use and risk of diabetes identified one relevant cross-sectional study [3], whose evidence was classified as weak based on the JBI critical appraisal score. Hu et al [3] investigated the association between THS use and prevalence of prediabetes (defined as fasting blood glucose [FBG] 100-125 mg/dL or HbA1c 5.7%-6.4%) and diabetes (defined as a FBG  $\geq 126$  mg/dL, HbA1c level  $\geq 6.5\%$ , or receipt of medical treatment for diabetes) in Japan. The authors analyzed the Japan Epidemiology Collaboration on Occupational Health data involving 8,950 workers from 5 companies (April 2018 to March 2021, Study I) and 31,341 workers from another large company (2021 onwards, Study II).

In a pooled analysis of Study I and II and compared to never CC smokers, former CC smokers (OR=1.21, 95%CI: 1.14-1.29), exclusive THS users (OR=1.36, 95%CI: 1.25-1.47), exclusive CC smokers (OR=1.12, 95%CI: 1.04-1.21), and dual users of THS and CC (OR=1.26, 95%CI: 1.13-1.39) had increased risk of prediabetes after adjusting for relevant factors. A similar, but stronger, pattern of association was reported for diabetes – former CC smokers (OR=1.22, 95%CI: 1.10-1.36), exclusive THS users (OR=1.68, 95%CI: 1.46-1.94), exclusive CC smokers (OR=1.57, 95%CI: 1.38-1.78), and dual users of THS and CC (OR=1.93, 95%CI: 1.62-2.29).

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