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Body-Mass Index in 2.3 Million Adolescents and Cardiovascular Death in Adulthood

Adolescent overweight and obesity have increased substantially in recent decades, affecting a quarter of the population in some developed countries, creating major concerns. Obesity early in life is considered a risk factor for all-cause mortality and cardiovascular disease mortality in midlife. Such large scale obesity epidemic may limit the anticipated increase in life expectancy otherwise achieved. Indeed, despite progress in prevention and treatment of cardiovascular disease, cardiovascular mortality among young adults has declined more slowly over recent decades in several developed countries coincident with the obesity epidemic. Some, although not all, studies suggest that body mass index (BMI) within the upper normal range in adolescence is associated with an increased risk for cardiovascular mortality, though there is uncertainty regarding specific BMI threshold associated with increased risk for adverse cardiovascular events.

Recently, the association between adolescence BMI and mortality attributed to cardiovascular mortality has been assessed in a large cohort of Israeli Adolescents. These studies were based on a national database of 2.3 million Israeli adolescents who were assessed prior to military conscription (mean age 17.3 ± 0.4 years, follow-up ranged between 1 to 44 years), measured from 1967-2010, whose records were linked to mortality data of the Israeli Ministry of Health. Primary outcomes were mortality by mid-2011 attributed to coronary heart disease, stroke, sudden death, and diabetes. As non-coronary non-stroke mortality of young adults has increased in recent years (as opposed to coronary mortality), mortality attributed to fatal arrhythmias, hypertensive heart disease, cardiomyopathies, arterial disease (dominated by aortic aneurysms), heart failure, and pulmonary embolism was also analyzed.

During 42,297,007 person-years of follow-up 1497, 528, 893 and 2,918 coronary, stroke, sudden deaths, respectively, occurred. Multivariable analysis showed a graded increase in all cardiovascular outcomes, and in non-cardiovascular and all-cause mortality starting in the

50th BMI percentile. There was a graded increase across the BMI categories for cardiovascular mortality. Hazard ratios for obesity ($\geq 95^{\text{th}}$ vs. 5th-24th percentiles) associated with mortality attributed to coronary, stroke, sudden death, diabetes and total cardiovascular mortality were 4.9 (95%CI 3.9-6.1), 2.6 (95%CI 1.7-4.1), 2.1 (95%CI 1.5-2.9), 17.2 (95%CI 11.9-24.8) and 4.1 (95%CI 3.5-4.9) respectively, adjusting for sex, age, birth year, socio-demographic characteristics and height. Applying multivariable-adjusted spline models, the estimated minimum risks of stroke, diabetes, sudden and cardiovascular deaths were at BMI values of 19.8, 17.7, 19.3 and 18.3 kg/m², respectively, whereas the association with coronary mortality was monotonic.

The findings persisted in a series of sensitivity analyses, including sex-specific analysis (which showed overall consistency between the sexes), restriction to adolescents with unimpaired health status, modelling the association with competing risks, restriction to examinees enrolled from 1967 to 1980, separate analysis for deaths occurring before and after age 45. There was a substantial population attributable fractions for coronary and cardiovascular mortality (calculated with an unverifiable assumption of causality). For BMI prevalence in the overweight obesity range, the projected population attributable fractions reach 20.4% for cardiovascular mortality and 27.4% for coronary heart disease mortality (using recent data regarding 2013 BMI data).

There were 279, 122, 121, 114, 94 and 70 deaths (25.2% of cardiovascular death) coded as fatal arrhythmias, hypertensive heart disease, cardiomyopathies, arterial disease (dominated by aortic aneurysms), heart failure, and pulmonary embolism, respectively, during follow-up period. BMI was positively associated with all study outcomes with hazard ratios (HRs) per 1 unit increment in BMI ranging from 1.09 (95%CI 1.03-1.16, $p=0.001$) for arterial disease to 1.16 (95%CI 1.11-1.21, $p=10^{-9}$) for hypertensive heart disease and exhibited an increased risk for BMI values above the 50th BMI percentile.

In conclusion, BMI in late adolescence, even within the currently accepted normal range, whether as an independent risk factor, a predictor of adult obesity, or both, is a strong predictor of cardiovascular and diabetes mortality in young adulthood and midlife. The secular 'shift to the right' in the adolescent BMI distribution and the rising prevalence of adolescent overweight and obesity may account for a substantial and increasing future burden of cardiovascular disease, particularly coronary heart disease.