**A GENOME-WIDE METHYLATION ANALYSIS SHOWS DIFFERENTIALLY METHYLATED REGIONS BETWEEN FUTURE CVD CASES AND CONTROLS**

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*Background*: Epigenetic factors are emerging as important cardiovascular disease (CVD) risk factors, with the advantage that they are dynamic and can be modified. Methylation is one of the main epigenetic factors, whose specific influence is still little known in CVD events. Moreover, not only environmental factors contribute to methylation levels, but also there are genetic factors.

*Objectives*: 1)To undertake a pilot epigenome-wide methylation study (EWAs) on a high cardiovascular risk Mediterranean population to detect at baseline the differentially methylated loci that are associated with future cardiovascular events; and 2)To discover SNPs that are associated with differences in methylation at those loci and could be proxies of the same.

*Methods*: A pilot EWAS was undertaken that included 12 subjects who had developed incident CVD throughout a median of 4.8 y of follow-up and 12 controls, paired by sex, diet and follow-up time, all being participants in the PREDIMED-Valencia study. An EWAS was undertaken to analyze the data from DNA methylation at baseline using the Infinium HumanMethylation450 BeadChip. The top-ranked methylation loci were identified and the SNPs of that gene analyzed. The SNPs were associated with methylation levels and the association of the most significant SNP with CVD incidence was studied in the 1,094 PREDIMED-Valencia study participants.

*Results and Conclusions*: The top-ranking methylation loci was the cg21585936 island in the PPP2R2B (protein phosphatase 2 regulatory subunit B, beta) gene. At baseline, cases had higher methylation levels than controls (+8%; P=0.000006). The SNP most associated with methylation levels was the PPP2R2B-rs3844538; with variant-allele carriers having lower methylation (P<0.025). Although in the subsample, the PPP2R2B-rs3844538 minor allele was associated with lower CVD incidence (P=0.014), this protection did not reach the statistical significance in the multivariable Cox regression model for the whole population (HR: 0.63; 95%CI: 0.25-1.61), suggesting additional modulation by environmental factors.