Dear Members of the International Atherosclerosis Society (IAS),

I would like to thank the IAS for supporting my 3-months fellowship as a visiting scientist in the Department of Epidemiology at the Harvard T.H. Chan School of Public Health. I would like to take the opportunity to express my deep gratitude towards my host Dr. Michelle Williams for welcoming me to her research team and for her invaluable guidance. I would also like to thank Dr. Bizu Gelaye for his continuous assistance and cooperation, and the team members for their hospitality.

My research interest lies in the field of genetic epidemiology, focusing on genetic and environmental risk factors for cardiometabolic risk (CMR) traits, including body mass index and waist circumference, glucose and insulin, lipids and lipoproteins, and blood pressure. I have a particular interest in the concept of “Developmental Origins of Health and Disease”, and for the past several years I have been studying the effects of early life exposures on adult cardiometabolic health, and its underlying genetic and epigenetic mechanisms. Ample evidence indicates that cardiovascular and other chronic diseases in adult life are influenced by intrauterine and early life exposures. For example, preterm birth, preeclampsia and birthweight have been consistently shown to be related to adult CMR traits and chronic diseases [1-7]. In recent years emerging data suggests that maternal overnutrition, reflected in part by greater maternal pre-pregnancy BMI (mppBMI) and gestational weight gain (GWG), may also impact offspring adiposity and related outcomes later in life [8,9].

Psychological stress as well as personality traits related to stress appraisal and coping skills have been linked to atherosclerosis and cardiovascular disease (CVD) [reviewed in 10,11]. As inflammation has an important contribution to atherosclerosis and also has a significant role in stress response, it has been suggested that inflammatory processes are mediating the association between stress and CVD [reviewed in 12]. For example, evidence demonstrates that the pro-inflammatory cytokine interleukin 1 (IL-1), produced following exposure to immunological and psychological challenges, plays an important role in the neuroendocrine and behavioral stress responses [13] and is also associated with CVD [14].

Early-life adverse experiences, such as abuse or neglect, are known to be related to the development of mental and behavioral disorders [reviewed in 15]. Several recent studies demonstrated that prenatal exposure to maternal psycho-social stress, measured either by adverse life events or exposure to acute life-threatening situations was associated with preterm delivery and birth weight and few studies also provide support for long-term associations with CMR traits, such as obesity and diabetes [reviewed in 16]. Although the mechanisms underlying the associations between intrauterine exposure to maternal stress and adult CMR are currently unknown, it has been suggested that here too increased inflammation may provide a causal link [16,17].

My previous work has demonstrated long-term associations of early-life exposures, including birth weight, gestational diabetes mellitus, maternal pre-pregnancy BMI, gestational weight gain and parental smoking during pregnancy, with various outcomes in adolescent and adult offspring, such as mortality [18] and CMR traits measured at age 17 and 32 [19-23]. We have also shown that
maternal genetic variation in a set of cardiometabolic candidate genes explained to some extent the associations between maternal GWG and offspring adiposity.\textsuperscript{20,21}

The IAS fellowship has provided me with a unique opportunity to gain experience in measuring and analyzing psychosocial data, allowing me to expand my research by incorporating psychological and behavioral factors into my ongoing research in cardiometabolic genetic epidemiology.

During my 3-month fellowship I worked on two major projects:

1) **Maternal exposure to violence and pregnancy outcomes**: This project is based on the ongoing Pregnancy Outcomes, Maternal and Infant Study (PrOMIS) Cohort, designed to examine maternal social and behavioral risk factors of preterm birth and other adverse pregnancy outcomes among Peruvian women. Enrolled participants were low-income pregnant Peruvian women receiving routine prenatal care who were invited to take part in an interview where trained research personnel used a structured questionnaire to elicit information regarding maternal socio-demographic, lifestyle characteristics, medical and reproductive histories, life experiences of childhood abuse and intimate partner abuse and symptoms of mood and anxiety disorders. Using this large sample (n≈2700), we assessed the associations of maternal exposure to violence and pregnancy outcomes, such as birth weight, and investigated whether there was evidence for a modifying effect of offspring sex and/or mediation by maternal depression status. The underlying hypothesis was that intrauterine exposure to maternal psychological stress induced by the mother’s exposure to childhood and/or adulthood violence may result in adverse pregnancy outcomes, which were shown to have long-term effects on offspring cardiometabolic health. Differential vulnerability of females and males in response to acute intrauterine stress was also reported in a few previous studies. Preliminary results in PrOMIS demonstrate associations between maternal exposure to violence, mainly intimate partner violence, and birth weight of male offspring. Additionally, suggestive evidence points to decreased male-to-female ratio among low birth weight newborns whose mothers were exposed to violence. These preliminary analyses thus serve as the initial piece in the causal pathway linking intrauterine exposure to psychological stress and subsequent cardiometabolic disease. The work is currently in progress and as data accumulates we will be able to examine additional pregnancy outcomes, such as preterm delivery, as well as the role of genetic variants in these associations.

2) **Maternal perinatal adiposity, offspring personality and cardiometabolic health**: This project is based on the Jerusalem Perinatal Study (JPS), a 1964-76 birth cohort of all 92,408 births to Israeli residents of West Jerusalem during this period. The JPS uniquely combines detailed archival records obtained at birth with comprehensive long-term follow-up data collected at age 32 among 1400 offspring from the original cohort. Using this sample we previously showed that maternal perinatal adiposity (i.e. maternal pre-pregnancy BMI and gestational weight gain) was associated with increased levels of offspring adiposity and related traits at age 32.\textsuperscript{19,20} During my IAS fellowship, I have expanded this investigation to examine whether maternal perinatal adiposity is related to offspring personality traits (i.e. type A personality), and whether personality characteristics mediate the previously demonstrated associations of maternal perinatal adiposity with offspring adiposity and related cardiometabolic traits. Preliminary results show the following: 1) maternal and offspring type A personality are correlated; 2) maternal type A personality is associated with gestational weight gain; and 3) offspring type A personality is related to adiposity
at age 32. Within the next few months we will also obtain genome-wide data on these 1440 offspring and using these genetic data we plan to assess whether genetic variation identified as related to cardiometabolic traits is also related to personality characteristics in our population.

In addition to these specific projects, I participated in Dr. William's weekly group meetings. The meetings allowed me to participate in stimulating and mind-opening discussions related to novel research questions and methodologies and provided me with insights on how to manage an efficient and productive research group. Furthermore, during my stay in Boston I also interacted with investigators from other institutions, such as Boston University and Massachusetts General Hospital, and I have been able to initiate new collaborations that I plan to follow-up on now that I am back in the Hebrew University. For example, based on initial discussions with sleep experts, we are planning to examine how a set of genes related to sleep contribute to perinatal and cardiometabolic outcomes in the JPS.

In sum, the IAS fellowship has contributed to advancing my research goal to develop an integrated and comprehensive scientific approach for the study of the early origins of adult cardiometabolic disease. It also allowed me to begin the process of developing new directions for investigating genetic and epigenetic mechanisms underlying associations of early-life exposures, psychological and behavioral factors with cardiometabolic health.

Equally important, the IAS fellowship served as an initial and necessary step in establishing a strong and long-lasting collaboration with Dr. Williams, and will hopefully consolidate firm working relations between the teams at Harvard T.H. Chan School of Public Health and the Hebrew University Braun School of Public Health.

Sincerely,

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References


