**Gene Expression in Pre-Disease Pathways:**
**The Importance of Life Course Patterns of BMI**

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**Abstract**
High levels of obesity in the United States and rising trends worldwide call for attention to the role of life course patterns of body mass index (BMI) in pre-disease pathways. Using recently collected mRNA abundance data in Wave 5 of the National Longitudinal Study of Adolescent to Adult Health (Add Health), this study examines how life course patterns of BMI are related to gene expression markers of important health outcomes in later life, including cardiac infarction, type 2 diabetes, and immune/inflammatory functioning as indicated by the conserved transcriptional response to adversity signature (CTRA). We test hypotheses using a Bayesian approach concerning different life course models: accumulation, critical, and sensitive periods. Preliminary results show a strong association between Wave V BMI and gene expression scores related to infarction and type 2 diabetes among people who have not had an infarction and do not have diabetes type 2, respectively.

**Introduction**
The integration of the social sciences and molecular genetics has proceeded at rapid pace, propelled largely by the development of appropriate statistical tools and the collection of DNA in representative samples such as the Health and Retirement Study, Add Health, Whitehall, and Framingham (Domingue et al. 2016). These advances have relied on Genome Wide Association Studies (GWAS), according to which, variation in base pairs (called single nucleotide polymorphisms, or SNPs) predict behavior and health outcomes. The GWAS approach has been profitably applied to the study of many classic concerns of the social sciences, including assortative mating (Conley et al. 2016), peer homophily (Domingue et al. 2018), social class (Belsky et al. 2018), reproductive behaviors (Beauchamp 2016; Mills et al. 2018), and longevity and mortality (Pilling et al. 2017; Yashin et al. 2016).

Recent advances in technology also allow for the collection of gene expression data in population-based studies, data that allow for a new perspective on the interplay between the genome and social forces. In contrast to GWAS, which focus on the invariant structure of the SNPs, gene expression data indicate how "active" genes are in synthesizing their products. Genes may be more or less active depending on, for example, regulatory elements that are upstream from the actual protein-coding region. Second, gene expression data shift the focus from how structural variation in SNPs predict outcomes to how social and physical circumstances ultimately impact these regulatory regions, turning specific gene sets "on" or "off" (upward and downward regulation). The social and physical environment cause changes in gene expression that, in turn, foster physiological adjustments to a person's surroundings but may also initiate and maintain disease processes. Moreover, the fundamental insight of GWAS is also retained: variation in expression patterns can then predict behaviors and health outcomes.

Although the expression of the genome is regulated by many mechanisms, early studies identified genetic transcription—the rate at which messenger RNA is "written out" from the DNA—as highly responsive to "signals" originating in social settings (Cole 2014). That is, social experiences "get under the skin" and influence the rate at which coding regions of the DNA are transcribed to mRNA, which in turn begins biological cascades regulating virtually

every biological process in the cell (Irwin & Cole, 2011). Research in psychoneuroimmunology points to diverse social experiences capable of triggering gene expression: social status, stressors, social isolation, social supports, geographic location, and stigma (Shanahan 2013). Genes associated with the immune system in monocytes in peripheral blood mononuclear cells appear to be quite responsive to these social factors, and these same genes can alter the probability of inflammatory and immune-related morbidities, including major causes of death in the West (e.g., hypertension, type 2 diabetes, some cancers, depression, and auto-immune disorders) (Franceschi and Campisi 2014) The study of gene transcription thus offers a strategic, mechanistic approach to how the organization of societies and systems biology combine to influence major forms of morbidity and mortality in populations.

In this paper, we explore the use of gene expression data (mRNA abundance) as indicators of pre-disease pathways, a concept proposed by Ryff and Singer (2001) to encompass the many contingencies that give rise to disease states before the appearance of clinically significant symptoms. The concept highlights the life course dimension of disease, with the probability of specific disease states already changing before birth and often continuing to change over many decades of life. The concept also recognizes that such pathways are highly multidimensional, encompassing social, psychological, cultural, economic, and biological levels of analysis.

We draw on mRNA abundance data collected as part of the ongoing Wave V of the National Longitudinal Study of Adolescent to Adult Health (Add Health) and interrelate these data to life-time patterns of body mass index (BMI), and anthropometric measures (such as waist circumference). BMI is a well-established, strong predictor of many disease states, including inflammatory morbidities, and emerging evidence shows that adipocytes are key players in inflammatory pathways (Smorlesi et al. 2012). We focus on mRNA signatures associated with infarction, type 2 diabetes, and immune/inflammatory patterns (CTRA) that may result in diseases. Very few Add Health respondents who are now in their late 30s have experienced an infarction, thus allowing us to examine associations between BMI and the activation of genes associated with the risk for infarctions before infarctions are experienced. We can similarly focus on mRNA diabetes 2 signature among those without clinical symptoms of that disease. To what extent does current BMI predict mRNA signatures of these disease states before they actually manifest in clinical symptoms? And to what extent do life-time patterns of BMI predict these signatures?

The concept of the pre-disease pathway is especially salient in the context of the Add Health cohort, which is among the first American youth cohorts to come of age during the obesity epidemic, yet have not yet reached the older adult ages at which diseases manifest widely in the population (Harris 2010). The cohort reflects trends in obesity, which have been increasing in prevalence and incidence for more than 20 years, calling for increased attention to the consequences for population health (Ogden et al. 2006; Yang and Colditz 2015). This is especially alarming for young people who have higher BMI compared to the previous cohorts, leading to higher prevalence of obesity in adulthood (Lee et al. 2011). Obesity is associated with many health issues as well as increased mortality rates (Dixon 2010; Flegal et al. 2013; Zajacova and Burgard 2010). Among the diseases related to higher BMI, previous research has highlighted especially the elevated risk of type 2 diabetes (Boone-Heinonen et al. 2018), cardiovascular diseases (Nordestgaard et al. 2012; Owen et al. 2009; Tirosh et al. 2011), cancer (Renehan et al. 2008) and systemic inflammation (Ellulu et al. 2017). The

increasing prevalence of overweight and obesity motivates the analysis of the gene expression associated with BMI at different points of the life course.

BMI changes greatly during the life-course showing a curvilinear relationship with age. Trajectories, timing, and changes in BMI over the life-course have been analyzed with reference to many different outcomes (Attard et al. 2013; Burdette and Needham 2012; The et al. 2013; Wickrama et al. 2014). However, the role of BMI at different points in the life course for the development of chronic diseases remains poorly understood (McCarron et al. 2000; Rademacher et al. 2009; Sakurai et al. 1999; Shihab et al. 2012). In order to examine the long-term effects of BMI during different periods, we use a typology of life course models suggested by Ben-Shlomo and Kuh (2004): accumulation, critical, and sensitive period models. The accumulation model posits that BMI in each life course phase contributes equally to health outcomes later in life. The critical and sensitive period models posit increased importance of BMI at specific points in the life, the former positing only one significant age period in the life course and the latter hypothesizing that some age periods have heightened salience. Variants of this models will also be examined.

**Data and Method**

Data for the preliminary analyses come from Wave V of Add Health, a nationally representative sample of adults aged 32 to 42 years. At Wave V, mRNA data were collected and analyzed from a random subsample of Add Health respondents (n=1132). Comparisons suggest that the mRNA subsample is similar to the overall sample in terms of BMI. There are no significant differences in BMI at Wave V between the mRNA subsample and the overall sample according to a Two-Samples Welch t-test.

Height and weight are either self-reported or measured by respondents at each wave. In particular, field examiners at waves II, III, IV, and V measured and collected height and weight for each respondent. Currently only self-reported BMI is available for Wave V, but physical exam data will become available by the time of PAA including waist circumference. Reliability of anthropometric measures collected in Add Health is high (Hussey et al. 2015). Moreover, we include measures of age, biological sex, race/ethnicity, and educational attainment collected at Wave 5. We include a sample-specific quality control measure for mRNA and indicators for assay batch (since observations collected in the same plate are expected to be highly correlated due to the lab methodology).

Three main gene expression signatures were constructed and analyzed: infarction, type 2 diabetes and conserved transcriptional response to adversity (CTRA). CTRA includes proinflammatory genes as well as genes involved in innate antiviral responses and antibody synthesis. The scores are constructed using an arithmetic mean of the expression scores for the genes that have been previously found to be associated with the different outcomes. The list of genes for infarction is derived from Poledne and Hubacek (2011), for diabetes from Xue et al. (2018), and for CTRA from Cole (2014). CTRA includes proinflammatory genes as well as genes involved in innate antiviral responses and antibody synthesis. The scores are constructed using an arithmetic mean of the expression scores for the genes that have been previously found to be associated with the different outcomes. We exclude from the analysis individuals who have experienced infarction or are diagnosed with type 2 diabetes at Wave V. In future analyses, these signatures will be examined using several methodologies, including a compositional approach (Erb and Notredame 2016).

In order to investigate which life course models best represent the data, we use a Bayesian approach for continuous exposure to different patterns of BMI (Madathil et al. 2018). Several models have been proposed in order to identify the best-fitting life course hypothesis (Ben-Shlomo et al. 2016; Mishra et al. 2009; Murray et al. 2016). The Bayesian approach proposed by Madathil et al. (2018) has many advantages compared to previous applications, such as direct estimation of the posterior probability for different hypotheses and no model selection. The preliminary results below are obtained from linear regression models. However, at PAA the results from the Bayesian approach will be presented.

**Preliminary results**

Tables 1 to 6 present the results using a linear regression model in order to test the association between BMI at Wave V and genetic expression scores related to infarction, diabetes, and CTRA. Results show that BMI at Wave V is strongly associated with the infarction (Table 1) and the diabetes mRNA risk signature (Table 2). The magnitude of the coefficient is small but highly significant. However, the size of the coefficient is not directly interpretable. CTRA and BMI at Wave V are unrelated (Table 3). Once the different components of CTRA are analyzed separately, BMI appears to be related to increasing expression of inflammatory genes (Table 4) but not the antibody and antiviral ones (Tables 5 and 6).

Table 1 – BMI and Infarction Gene Expression at Wave V (ages 32-42)

| | **Infarction Signature** | | **Infarction Signature** | |
|---|---|---|---|---|
| *Predictors* | *Estimates* | *p* | *Estimates* | *p* |
| Intercept | 0.06 | 0.891 | 0.09 | 0.846 |
| BMI Wave V | 0.00 | **<0.001** | 0.00 | **<0.001** |
| | | | | |
| Male | -0.01 | 0.411 | -0.01 | 0.354 |
| Black (ref. White) | 0.02 | 0.283 | 0.02 | 0.318 |
| Native | 0.03 | 0.438 | 0.03 | 0.378 |
| Asian | -0.02 | 0.751 | -0.02 | 0.791 |
| Other Race | 0.01 | 0.547 | 0.01 | 0.684 |
| Current Smoker | 0.06 | **<0.001** | 0.05 | **0.006** |
| Drinks everyday | -0.01 | 0.610 | -0.01 | 0.772 |
| Plate2 | -0.06 | 0.116 | -0.06 | 0.106 |
| Plate3 | -0.05 | 0.222 | -0.05 | 0.199 |
| Plate4 | -0.05 | 0.212 | -0.05 | 0.210 |
| Plate5 | 0.08 | **0.042** | 0.08 | **0.045** |
| Plate6 | 0.05 | 0.185 | 0.05 | 0.176 |
| Plate7 | 0.00 | 0.915 | 0.00 | 0.997 |
| Plate8 | 0.04 | 0.284 | 0.04 | 0.305 |
| Plate9 | -0.08 | **0.036** | -0.08 | **0.043** |
| Plate10 | -0.12 | **0.003** | -0.12 | **0.003** |
| Plate11 | 0.07 | 0.063 | 0.07 | 0.069 |
| Plate12 | -0.02 | 0.576 | -0.02 | 0.539 |
| Quality | 3.29 | **<0.001** | 3.26 | **<0.001** |
| Age | -0.00 | 0.386 | -0.00 | 0.377 |
| HS | | | 0.03 | 0.067 |
| Less-than-HS | | | 0.01 | 0.763 |
| Observations | 916 | | 916 | |
| $R^2$ / adjusted $R^2$ | 0.164 / 0.144 | | 0.167 / 0.146 | |

Table 2 – BMI and Diabetes' Gene Expression at Wave V (ages 32-42)

| | **Diabetes' Signature** | | **Diabetes' Signature** | |
|---|---|---|---|---|
| *Predictors* | *Estimates* | *p* | *Estimates* | *p* |
| Intercept | -0.63 | 0.229 | -0.60 | 0.249 |
| BMI Wave V | 0.01 | **<0.001** | 0.01 | **<0.001** |
| Male | 0.00 | 0.975 | -0.00 | 0.964 |
| Black (ref. White) | 0.08 | **<0.001** | 0.08 | **<0.001** |
| Native | 0.01 | 0.786 | 0.01 | 0.719 |
| Asian | 0.06 | 0.502 | 0.06 | 0.476 |
| Other Race | 0.03 | 0.240 | 0.03 | 0.294 |
| Current Smoker | 0.07 | **0.001** | 0.06 | **0.004** |
| Drinks everyday | 0.02 | 0.433 | 0.02 | 0.351 |
| Plate2 | 0.00 | 0.978 | 0.00 | 0.998 |
| Plate3 | 0.04 | 0.419 | 0.03 | 0.452 |
| Plate4 | -0.02 | 0.555 | -0.02 | 0.556 |
| Plate5 | -0.02 | 0.567 | -0.03 | 0.546 |
| Plate6 | 0.03 | 0.487 | 0.03 | 0.481 |
| Plate7 | 0.08 | 0.057 | 0.08 | 0.068 |
| Plate8 | 0.08 | 0.090 | 0.08 | 0.094 |
| Plate9 | -0.38 | **<0.001** | -0.38 | **<0.001** |
| Plate10 | -0.42 | **<0.001** | -0.42 | **<0.001** |
| Plate11 | -0.09 | **0.025** | -0.10 | **0.025** |
| Plate12 | -0.23 | **<0.001** | -0.23 | **<0.001** |
| Quality | 6.74 | **<0.001** | 6.71 | **<0.001** |
| Age | -0.01 | 0.223 | -0.01 | 0.218 |
| HS | | | 0.02 | 0.192 |
| Less-than-HS | | | -0.00 | 0.998 |
| Observations | 876 | | 876 | |
| $R^2$ / adjusted $R^2$ | 0.293 / 0.275 | | 0.294 / 0.275 | |

Table 3 – BMI and CTRA Gene Expression at Wave V (ages 32-42)

| | **M1** | | **M2** | |
|---|---|---|---|---|
| *Predictors* | *Estimates* | *p* | *Estimates* | *p* |
| Intercept | -4.18 | **0.002** | -4.16 | **0.002** |
| BMI Wave V | -0.00 | 0.612 | -0.00 | 0.492 |
| Male | 0.22 | **<0.001** | 0.21 | **<0.001** |
| Black (ref. White) | -0.07 | 0.273 | -0.07 | 0.248 |
| Native | -0.25 | **0.019** | -0.24 | **0.023** |
| Asian | -0.26 | 0.202 | -0.25 | 0.217 |
| Other Race | -0.04 | 0.546 | -0.05 | 0.466 |
| Current Smoker | 0.02 | 0.717 | -0.00 | 0.985 |
| Drinks everyday | -0.17 | **0.004** | -0.16 | **0.006** |
| Plate2 | 0.04 | 0.694 | 0.04 | 0.713 |
| Plate3 | 0.00 | 0.977 | 0.00 | 0.988 |
| Plate4 | 0.13 | 0.242 | 0.13 | 0.244 |
| Plate5 | -0.06 | 0.585 | -0.06 | 0.581 |
| Plate6 | 0.13 | 0.251 | 0.13 | 0.246 |
| Plate7 | 0.02 | 0.890 | 0.01 | 0.928 |
| Plate8 | 0.17 | 0.147 | 0.17 | 0.150 |
| Plate9 | -0.32 | **0.004** | -0.32 | **0.005** |
| Plate10 | -0.18 | 0.121 | -0.18 | 0.124 |
| Plate11 | -0.26 | **0.018** | -0.27 | **0.017** |
| Plate12 | -0.11 | 0.323 | -0.11 | 0.301 |
| Quality | 4.31 | **0.002** | 4.30 | **0.002** |
| Age | -0.01 | 0.578 | -0.01 | 0.563 |
| HS | | | 0.05 | 0.293 |
| Less-than-HS | | | 0.08 | 0.574 |
| Observations | 927 | | 927 | |
| $R^2$ / adjusted $R^2$ | 0.071 / 0.049 | | 0.072 / 0.049 | |

Table 4 – BMI and Inflammatory Gene Expression (CTRA's component 1) at Wave V (ages 32-42)

| | **M1** | | **M2** | |
|---|---|---|---|---|
| *Predictors* | *Estimates* | *p* | *Estimates* | *p* |
| Intercept | 0.81 | 0.059 | 0.82 | 0.055 |
| BMI Wave V | 0.00 | <0.001 | 0.00 | <0.001 |
| Male | -0.04 | 0.003 | -0.04 | 0.003 |
| Black (ref. White) | 0.09 | <0.001 | 0.09 | <0.001 |
| Native | 0.07 | 0.027 | 0.07 | 0.026 |
| Asian | 0.04 | 0.551 | 0.04 | 0.558 |
| Other Race | 0.04 | 0.073 | 0.04 | 0.076 |
| Current Smoker | 0.04 | 0.027 | 0.04 | 0.042 |
| Drinks everyday | -0.02 | 0.274 | -0.02 | 0.289 |
| Plate2 | -0.02 | 0.648 | -0.02 | 0.646 |
| Plate3 | 0.06 | 0.096 | 0.06 | 0.107 |
| Plate4 | -0.03 | 0.330 | -0.03 | 0.332 |
| Plate5 | -0.03 | 0.351 | -0.03 | 0.337 |
| Plate6 | 0.04 | 0.202 | 0.05 | 0.200 |
| Plate7 | 0.08 | 0.026 | 0.08 | 0.028 |
| Plate8 | 0.09 | 0.020 | 0.09 | 0.022 |
| Plate9 | -0.37 | <0.001 | -0.37 | <0.001 |
| Plate10 | -0.36 | <0.001 | -0.36 | <0.001 |
| Plate11 | -0.06 | 0.065 | -0.06 | 0.076 |
| Plate12 | -0.14 | <0.001 | -0.14 | <0.001 |
| Quality | 4.94 | <0.001 | 4.92 | <0.001 |
| Age | -0.00 | 0.655 | -0.00 | 0.676 |
| HS | | | 0.01 | 0.614 |
| Less-than-HS | | | -0.04 | 0.377 |
| Observations | 927 | | 927 | |
| $R^2$ / adjusted $R^2$ | 0.288 / 0.271 | | 0.289 / 0.271 | |

Table 5 – BMI and Antibody Gene Expression (CTRA's component 2) at Wave V (ages 32-42)

| | **M1** | | **M2** | |
|---|---|---|---|---|
| *Predictors* | *Estimates* | *p* | *Estimates* | *p* |
| Intercept | 1.66 | 0.083 | 1.65 | 0.085 |
| BMI Wave V | 0.00 | 0.284 | 0.00 | 0.219 |
| Male | -0.04 | 0.212 | -0.04 | 0.240 |
| Black (ref. White) | 0.06 | 0.178 | 0.06 | 0.160 |
| Native | 0.02 | 0.813 | 0.01 | 0.865 |
| Asian | 0.22 | 0.125 | 0.21 | 0.135 |
| Other Race | 0.07 | 0.184 | 0.07 | 0.150 |
| Current Smoker | -0.01 | 0.715 | -0.00 | 0.993 |
| Drinks everyday | 0.08 | 0.062 | 0.07 | 0.084 |
| Plate2 | -0.00 | 0.978 | -0.00 | 0.997 |
| Plate3 | 0.05 | 0.574 | 0.05 | 0.568 |
| Plate4 | -0.06 | 0.415 | -0.06 | 0.417 |
| Plate5 | 0.06 | 0.425 | 0.06 | 0.422 |
| Plate6 | -0.00 | 0.951 | -0.01 | 0.942 |
| Plate7 | 0.04 | 0.618 | 0.04 | 0.589 |
| Plate8 | 0.03 | 0.760 | 0.03 | 0.756 |
| Plate9 | 0.16 | 0.054 | 0.15 | 0.057 |
| Plate10 | 0.02 | 0.834 | 0.02 | 0.840 |
| Plate11 | -0.03 | 0.748 | -0.02 | 0.782 |
| Plate12 | -0.01 | 0.868 | -0.01 | 0.906 |
| Quality | -1.55 | 0.110 | -1.55 | 0.111 |
| Age | -0.01 | 0.530 | -0.01 | 0.547 |
| HS | | | -0.03 | 0.341 |
| Less-than-HS | | | -0.06 | 0.556 |
| Observations | 927 | | 927 | |
| $R^2$ / adjusted $R^2$ | 0.027 / 0.004 | | 0.028 / 0.003 | |

Table 6 – BMI and Interferon Type I Gene Expression (CTRA's component 3) at Wave V (ages 32-42)

| | **M1** | | **M2** | |
|---|---|---|---|---|
| *Predictors* | *Estimates* | *p* | *Estimates* | *p* |
| Intercept | 3.33 | 0.001 | 3.33 | 0.001 |
| BMI Wave V | 0.00 | 0.224 | 0.00 | 0.203 |
| Male | -0.22 | <0.001 | -0.22 | <0.001 |
| Black (ref. White) | 0.10 | 0.035 | 0.10 | 0.032 |
| Native | 0.30 | <0.001 | 0.30 | <0.001 |
| Asian | 0.08 | 0.609 | 0.07 | 0.625 |

| | | | | |
|---|---|---|---|---|
| Other Race | 0.02 | 0.758 | 0.02 | 0.716 |
| Current Smoker | 0.03 | 0.423 | 0.04 | 0.369 |
| Drinks everyday | 0.07 | 0.096 | 0.07 | 0.111 |
| Plate2 | -0.06 | 0.486 | -0.06 | 0.493 |
| Plate3 | 0.01 | 0.895 | 0.01 | 0.905 |
| Plate4 | -0.10 | 0.226 | -0.10 | 0.227 |
| Plate5 | -0.04 | 0.673 | -0.04 | 0.668 |
| Plate6 | -0.08 | 0.345 | -0.08 | 0.343 |
| Plate7 | 0.02 | 0.774 | 0.02 | 0.768 |
| Plate8 | -0.11 | 0.208 | -0.11 | 0.206 |
| Plate9 | -0.20 | 0.018 | -0.20 | 0.019 |
| Plate10 | -0.19 | 0.024 | -0.19 | 0.025 |
| Plate11 | 0.22 | 0.007 | 0.23 | 0.006 |
| Plate12 | -0.02 | 0.783 | -0.02 | 0.812 |
| Quality | 2.19 | 0.032 | 2.17 | 0.033 |
| Age | 0.01 | 0.248 | 0.01 | 0.240 |
| HS | | | -0.01 | 0.769 |
| Less-than-HS | | | -0.06 | 0.568 |
| Observations | 927 | | 927 | |
| $R^2$ / adjusted $R^2$ | 0.098 / 0.078 | | 0.099 / 0.076 | |

**Preliminary Conclusions**

The aim of this analysis is to understand how life course patterns of BMI are related to mRNA risk signatures of important health outcomes in later life. Preliminary results suggest that contemporaneous BMI at ages 32-42 is especially related to enhanced expression for genes associated with infarction, type 2 diabetes, and inflammation. Further analysis will apply a Bayesian approach to test three hypotheses related to the relevance of BMI life course pattern for pre-disease markers. In which part of the life course will BMI matter the most for the expression of genes related to these different diseases? Understanding when in pre-disease pathways BMI matters the most can be helpful for designing effective policy interventions to reduce the impact of obesity on public health outcomes.

This work is not free from limitations. First, the design does not allow us to make causal statements about BMI. Second, the gene expression scores are markers of pre-disease, but they are probabilistic and the degree of their specificity and sensitivity is presently unknown. Finally, a more extensive characterization of BMI, including birthweight, would be ideal. Nevertheless, the present is the first to examine associations between BMI and mRNA risk signatures for major forms of mortality in a population-based study, and the results suggest a social and biologically plausible pathway by which gene expression can identify people at risk for later disease.

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