Supplemental Table 1. Clinical characteristics of Framingham Offspring participants at Exam 8 and Third Generation participants at Exam 2 by generation and sex.

Characteristics[1]	Offspring		Third Generation	
	Men (n=990)	Women (n=1230)	Men (n=1338)	Women (n=1603)
Age,years	66 ± 9	66 ± 9	47 ± 9	46 ± 9
DGAI score	57.6 ± 11.2	62.9 ± 11.4	56.9 ± 11.2	64.3 ± 10.0
BMI, kg/m2	29 ±5	28 ± 6	29 ± 5	27 ± 6
Current smoking, %	70 (7.1)	101 (8.2)	53 (4.0)	50 (3.1)
Hypertension, %	682 (68.9)	723 (53.8)	378 (28.5)	275 (17.1)
Diabetes, %	197 (19.9)	165 (13.4)	82 (6.1)	57 (3.6)
Total cholesterol, mg/dL	173 ± 35	196 ± 36	187 ± 37	186 ± 35
HDL cholesterol, mg/dL	50 ± 14	64 ± 18	51 ± 14	67 ± 17
Lipid treatment, %	490 (49.5)	485 (39.4)	310 (23.1)	166 (10.4)
Physical activity index	35.7 ± 6.1	34.9 ± 4.5	37.2 ± 7.9	35.7 ± 5.1
Pack-years	18.0 ± 23.2	12.6 ± 19.0	10.4 ± 18.8	8.7 ± 15.9
Cardiovascular disease, %	207 (20.9)	149 (12.1)	47 (3.5)	26 (1.6)
Energy intake, kcal/day	1969± 670	1789 ± 602	2092 ± 660	1907 ± 599

[1]Data are represented as Mean ± SD for continuous values, or N (%) for categorical values
DGAI: Dietary Guidelines for Americans Adherence Index; BMI: body mass index; HDL: high-density lipoprotein

Supplemental Table 2. The association of top DGAI-related genes among never smokers (N=2455) or no current smokers (N=4544). The association was assessed by linear mixed effect models adjusted for age, sex, imputed cell counts, and technical covariates.

Gene	Never smokers (N=2455)			No current smokers (N=4544)		
	Beta	**SE**	***P* value**	**Beta**	**SE**	***P* value**
ARRDC3	0.0020	0.0005	$2.6x10^{-5}$	0.0015	0.0003	$9.2x10^{-6}$
SIX4	0.0010	0.0004	$9.8x10^{-3}$	0.0011	0.0003	$6.1x10^{-5}$
PKN2	0.0011	0.0003	$9.2x10^{-4}$	0.0010	0.0002	$3.4x10^{-5}$
RNF141	0.0013	0.0005	$1.1x10^{-2}$	0.0013	0.0004	$3.0x10^{-4}$
NOLC1	-0.0011	0.0005	$1.8x10^{-2}$	-0.0012	0.0003	$3.0x10^{-4}$
STAG1	0.0008	0.0003	$3.4x10^{-3}$	0.0008	0.0002	$4.9x10^{-5}$
DNAJA1	-0.0014	0.0004	$5.8x10^{-4}$	-0.0012	0.0003	$1.3x10^{-4}$
MIER1	0.0009	0.0003	$9.1x10^{-3}$	0.0009	0.0002	$2.7x10^{-4}$
G0S2	0.0030	0.0009	$1.2x10^{-3}$	0.0024	0.0007	$2.7x10^{-4}$
PTP4A1	0.0017	0.0004	$6.4x10^{-5}$	0.0012	0.0003	$1.6x10^{-4}$
EXOC8	0.0011	0.0003	$1.0x10^{-3}$	0.0010	0.0002	$3.7x10^{-5}$
FAM116A	0.0015	0.0004	$1.5x10^{-5}$	0.0011	0.0003	$2.7x10^{-5}$
HIST1H2AE	0.0018	0.0010	$6.0x10^{-2}$	0.0024	0.0007	$5.2x10^{-4}$
IER3	0.0014	0.0004	$4.9x10^{-4}$	0.0011	0.0003	$4.3x10^{-4}$
SNX13	0.0010	0.0004	$5.3x10^{-3}$	0.0008	0.0003	$1.1x10^{-3}$
CYB5R4	0.0009	0.0004	$1.4x10^{-2}$	0.0011	0.0003	$1.2x10^{-4}$
RFWD2	0.0011	0.0004	$3.5x10^{-3}$	0.0010	0.0003	$9.0x10^{-5}$
CCDC126	0.0017	0.0006	$3.8x10^{-3}$	0.0015	0.0004	$4.4x10^{-4}$
HSPH1	-0.0015	0.0005	$1.6x10^{-3}$	-0.0013	0.0003	$2.0x10^{-4}$

DGAI: Dietary Guidelines for Americans Adherence Index; SE: standard error

Supplemental Table 3. Top 10 biological pathways enriched with genes in the DGAI-specific subnetwork

Biological process	**Total number of genes in pathway**	**Ratio of enrichment**	***P* value**	**False discovery rate (FDR)**	**Overlapping genes in the pathway**
Epstein-Barr virus infection	204	8.77	1.1×10^{-7}	3.4×10^{-5}	*HDAC5; CSNK2A1; AKT1; HDAC1; HSPA8; NEDD4; POLR1D; XPO1; YWHAZ; USP7*
Cell cycle	124	8.66	5.6×10^{-5}	7.6×10^{-3}	*STAG1; E2F4; HDAC1; SMAD2; YWHAZ; CCNH*
Endocytosis	260	5.51	7.5×10^{-5}	7.6×10^{-3}	*PDCD6IP; ADRB2; NEDD4L; HSPA8; SMAD2; ARRB2; NEDD4; SMURF1*
Estrogen signaling pathway	100	8.95	2.1×10^{-4}	1.6×10^{-2}	*AKT1; GNAS; HSPA8; SP1; CALM1*
Dopaminergic synapse	130	6.88	7.2×10^{-4}	3.5×10^{-2}	*AKT1; GNAS; ARRB2; GNG2; CALM1*
FoxO signaling pathway	134	6.68	8.3×10^{-4}	3.5×10^{-2}	*AKT1; SMAD2; PTEN; USP7; TNFSF10*
Measles	136	6.58	8.8×10^{-4}	3.5×10^{-2}	*CSNK2A1; AKT1; HSPA8; TNFSF10; TNFRSF10C*
Ubiquitin mediated proteolysis	137	6.53	9.1×10^{-4}	3.5×10^{-2}	*NEDD4L; NEDD4; SMURF1; RFWD2; CUL4A*
TGF-beta signaling pathway	84	8.52	1.2×10^{-3}	3.9×10^{-2}	*E2F4; SMAD2; SMURF1; SP1*
Pathways in cancer	397	3.61	1.3×10^{-3}	4.0×10^{-2}	*CEBPA; AKT1; GNAS; HDAC1; SMAD2; GNG2; PTEN; CASP3*

DGAI: Dietary Guidelines for Americans Adherence Index

Supplemental Table 4. Description of top 10 biological pathways enriched with genes in the DGAI-specific subnetwork

Pathway ID	Pathway	Description
hsa05169	Epstein-Barr virus infection	Epstein-Barr virus (EBV) is a gamma-herpes virus that widely infects human populations predominantly at an early age but remains mostly asymptomatic. EBV has been linked to a wide spectrum of human malignancies, including nasopharyngeal carcinoma and other hematologic cancers, like Hodgkin's lymphoma, Burkitt's lymphoma (BL), B-cell immunoblastic lymphoma in HIV patients, and posttransplant-associated lymphoproliferative diseases. EBV has the unique ability to establish life-long latent infection in primary human B lymphocytes. During latent infection, EBV expresses a small subset of genes, including 6 nuclear antigens (EBNA-1, -2, -3A, -3B, -3C, and -LP), 3 latent membrane proteins (LMP-1, -2A, and -2B), 2 small noncoding RNAs (EBER-1 and 2). On the basis of these latent gene expression, three different latency patterns associated with the types of cancers are recognized.
hsa04110	Cell cycle	Mitotic cell cycle progression is accomplished through a reproducible sequence of events, DNA replication (S phase) and mitosis (M phase) separated temporally by gaps known as G1 and G2 phases. Cyclin-dependent kinases (CDKs) are key regulatory enzymes, each consisting of a catalytic CDK subunit and an activating cyclin subunit. CDKs regulate the cell's progression through the phases of the cell cycle by modulating the activity of key substrates. Downstream targets of CDKs include transcription factor E2F and its regulator Rb. Precise activation and inactivation of CDKs at specific points in the cell cycle are required for orderly cell division. Cyclin-CDK inhibitors (CKIs), such as p16Ink4a, p15Ink4b, p27Kip1, and p21Cip1, are involved in the negative regulation of CDK activities, thus providing a pathway through which the cell cycle is negatively regulated. Eukaryotic cells respond to DNA damage by activating signaling pathways that promote cell cycle arrest and DNA repair. In response to DNA damage, the checkpoint kinase ATM phosphorylates and activates Chk2, which in turn directly phosphorylates and activates p53 tumor suppressor protein. p53 and its transcriptional targets play an important role in both G1 and G2 checkpoints. ATR-Chk1-mediated protein degradation of Cdc25A protein phosphatase is also a mechanism conferring intra-S-phase checkpoint activation.
hsa04144	Endocytosis	Endocytosis is a mechanism for cells to remove ligands, nutrients, and plasma membrane (PM) proteins, and lipids from the cell surface, bringing them into the cell interior. Transmembrane proteins entering through clathrin-dependent endocytosis (CDE)

		have sequences in their cytoplasmic domains that bind to the APs (adaptor-related protein complexes) and enable their rapid removal from the PM. In addition to APs and clathrin, there are numerous accessory proteins including dynamin. Depending on the various proteins that enter the endosome membrane, these cargoes are sorted to distinct destinations. Some cargoes, such as nutrient receptors, are recycled back to the PM. Ubiquitylated membrane proteins, such as activated growth-factor receptors, are sorted into intraluminal vesicles and eventually end up in the lysosome lumen via multivesicular endosomes (MVEs). There are distinct mechanisms of clathrin-independent endocytosis (CIE) depending upon the cargo and the cell type.
hsa04915	Estrogen signaling pathway	Estrogens are steroid hormones that regulate a plethora of physiological processes in mammals, including reproduction, cardiovascular protection, bone integrity, cellular homeostasis, and behavior. Estrogen mediates its cellular actions through two signaling pathways classified as "nuclear-initiated steroid signaling" and "membrane-initiated steroid signaling". In the "nuclear" pathway, estrogen binds either ERalpha or ERbeta, which in turn translocates to the nucleus, binds DNA at ERE elements and activates the expression of ERE-dependent genes. In "membrane" pathway, Estrogen can exert its actions through a subpopulation of ER at the plasma membrane (mER) or novel G-protein coupled E2 receptors (GPER). Upon activation of these receptors various signaling pathways (i.e. Ca2+, cAMP, protein kinase cascades) are rapidly activated and ultimately influence downstream transcription factors.
hsa04728	Dopaminergic synapse	Dopamine (DA) is an important and prototypical slow neurotransmitter in the mammalian brain, where it controls a variety of functions including locomotor activity, motivation and reward, learning and memory, and endocrine regulation. Once released from presynaptic axonal terminals, DA interacts with at least five receptor subtypes in the central nervous system (CNS), which have been divided into two groups: the D1-like receptors (D1Rs), comprising D1 and D5 receptors, both positively coupled to adenylyl cyclase and cAMP production, and the D2-like receptors (D2Rs), comprising D2, D3, and D4 receptors, whose activation results in inhibition of adenylyl cyclase and suppression of cAMP production. In addition, D1Rs and D2Rs modulate intracellular Ca2+ levels and a number of Ca2+ -dependent intracellular signaling processes. Through diverse cAMP- and Ca2+-dependent and - independent mechanisms, DA influences neuronal activity, synaptic plasticity, and behavior. Presynaptically localized D2Rs regulate synthesis and release of DA as the main autoreceptor of the dopaminergic system.

hsa04068	FoxO signaling pathway	The forkhead box O (FOXO) family of transcription factors regulates the expression of genes in cellular physiological events including apoptosis, cell-cycle control, glucose metabolism, oxidative stress resistance, and longevity. A central regulatory mechanism of FOXO proteins is phosphorylation by the serine-threonine kinase Akt/protein kinase B (Akt/PKB), downstream of phosphatidylinositol 3-kinase (PI3K), in response to insulin or several growth factors. Phosphorylation at three conserved residues results in the export of FOXO proteins from the nucleus to the cytoplasm, thereby decreasing expression of FOXO target genes. In contrast, the stress-activated c-Jun N-terminal kinase (JNK) and the energy sensing AMP-activated protein kinase (AMPK), upon oxidative and nutrient stress stimuli phosphorylate and activate FoxOs. Aside from PKB, JNK and AMPK, FOXOs are regulated by multiple players through several post-translational modifications, including phosphorylation, but also acetylation, methylation and ubiquitylation.
hsa05162	Measles	Measles virus (MV) is highly contagious virus that leads infant death worldwide. Humans are the unique natural reservoir for this virus. It causes severe immunosuppression favouring secondary bacterial infections. Several MV proteins have been suggested to disturb host immunity. After infection of host lymphoid cells via SLAM, MV inhibits cytokine response by direct interference with host signaling systems. Three proteins (P, V, and C) associate with Jak/STAT proteins in interferon-triggered pathway and other important proteins related to apoptosis. Interaction between MV and host brings about the shift towards a Th2 response by decreasing IL-12 production and induces lymphopenia by suppressing cell proliferation.
hsa04120	Ubiquitin mediated proteolysis	Protein ubiquitination plays an important role in eukaryotic cellular processes. It mainly functions as a signal for 26S proteasome dependent protein degradation. The addition of ubiquitin to proteins being degraded is performed by a reaction cascade consisting of three enzymes, named E1 (ubiquitin activating enzyme), E2 (ubiquitin conjugating enzyme), and E3 (ubiquitin ligase). Each E3 has specificity to its substrate, or proteins to be targeted by ubiquitination. Many E3s are discovered in eukaryotes and they are classified into four types: HECT type, U-box type, single RING-finger type, and multi-subunit RING-finger type. Multi-subunit RING-finger E3s are exemplified by cullin-Rbx E3s and APC/C. They consist of a RING-finger-containing subunit (RBX1 or RBX2) that functions to bind E2s, a scaffold-like cullin molecule, adaptor proteins, and a target recognizing subunit that binds substrates.
hsa04350	TGF-beta signaling	The transforming growth factor-beta (TGF-beta) family members, which include TGF-betas, activins and bone morphogenetic

	pathway	proteins (BMPs), are structurally related secreted cytokines found in species ranging from worms and insects to mammals. A wide spectrum of cellular functions such as proliferation, apoptosis, differentiation and migration are regulated by TGF-beta family members. TGF-beta family member binds to the Type II receptor and recruits Type I, whereby Type II receptor phosphorylates and activates Type I. The Type I receptor, in turn, phosphorylates receptor-activated Smads (R-Smads: Smad1, Smad2, Smad3, Smad5, and Smad8). Once phosphorylated, R-Smads associate with the co-mediator Smad, Smad4, and the heteromeric complex then translocates into the nucleus. In the nucleus, Smad complexes activate specific genes through cooperative interactions with other DNA-binding and coactivator (or co-repressor) proteins.
hsa05200	Pathways in cancer	Cancer related pathways

Supplemental Figure 1. Participant flowchart