SUPPLEMENT: Interactions of dietary whole grain intake with fasting glucose- and insulin-related genetic loci in individuals of European descent: a meta-analysis of 14 cohort studies

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The ***H**ealth, **A**ging and **B**ody **C**omposition* (**Health ABC**) study was supported in part by the Intramural Research Program of the NIH, National Institute on Aging contracts N01AG62101, N01AG62103, and N01AG62106. The genome-wide association study was funded by NIA grant R01 AG032098 to Wake Forest University Health Sciences and genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268200782096C.
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The ***C**ardiovascular **H**ealth **S**tudy* (**CHS**) research reported in this article was supported by contract numbers N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, grant numbers U01 HL080295 and R01 HL087652 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm. DNA handling and genotyping was supported in part by National Center for Research Resources grant M01RR00069 to the Cedars-Sinai General Clinical Research Center Genotyping core and National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center.
[representing authors: RNL, LD, KM, DM, KR, JR, DSS]

The *Framingham Offspring Study* and *Framingham Third Generation Study* (**FHS**) were conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. Also supported by National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) R01 DK078616 to Drs. Meigs, Dupuis and Florez, NIDDK K24 DK080140 to Dr. Meigs, and a Massachusetts General Hospital Physician Scientist Development Award and a Doris Duke Charitable Foundation Clinical Scientist Development Award to Dr. Florez. Dr. Hivert was supported by the Centre de Recherche Medicale de l'Universite de Sherbrooke (CRMUS) and a Canadian Institute of Health Research (CHIR) Fellowships Health Professional Award. Dr. Nicola McKeown is supported by the USDA agreement No. 58-1950-7-707.
[representing authors: NM, MFH, JN, AC, JD, JMO, JBM]

The ***A**therosclerosis **R**isk in **C**ommunities* (**ARIC**) study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. Dr. Nettleton is supported by a K01 from the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (5K01DK082729-02).
[representing authors: JAN, JLF, JSP]

The ***F**amily **H**eart **S**tudy* (**FamHS**) work was supported in part by NIH grants 5R01 HL08770003, 5R01 HL08821502 (Michael A. Province) from NHLBI, and 5R01 DK07568102, 5R01 DK06833603 from NIDDK (Ingrid B. Borecki), and by the National Heart, Lung, and Blood Institute cooperative agreement grants U01 HL 67893, U01 HL67894, U01 HL67895, U01 HL67896, U01 HL67897, U01 HL67898, U01 HL67899, U01 HL67900, U01 HL67901, U01 HL67902, U01 HL56563, U01 HL56564, U01 HL56565, U01 HL56566, U01 HL56567, U01 HL56568, and U01 HL56569. The investigators thank the staff and participants of the FHS for their important contributions.
[representing authors: MKW, LD, MFF, IB]

The ***A**ge, **G**ene, and **E**nvironment **S**usceptibility* (**AGES**) study is funded by NIH contract N01-AG-12100, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). Genotyping was conducted at the NIA IRP Laboratory of Neurogenetics.
[representing authors: MG, TT, LJL, MAN, AS, LS]

The ***Fenland** Study* is funded by the Wellcome Trust and the Medical Research Council. We are grateful to all the volunteers for their time and help and to the General Practitioners and practice staff for help with recruitment. We thank the Fenland Study co-ordination team, the Field Epidemiology team, and the Fenland Study investigators. Biochemical assays were performed by the National Institute for Health Research, Cambridge Biomedical Research Centre, Core Biochemistry Assay Laboratory, and the Cambridge University Hospitals NHS Foundation Trust.
[representing authors: ZY, NF, CL, RL, NW]

The *Malmö Diet & Cancer Study,* (**Malmö**) was initiated and planned in collaboration with the International Agency for Research on Cancer, the Swedish Cancer Society, and Swedish Medical Research Council and the Faculty of Medicine Lund University, Sweden. The study is also funded by Region Skåne, City of Malmö, Påhlsson Foundation and the Swedish Heart and Lung Foundation.
[representing authors: ES, MOM]

***U**ppsala **L**ongitudinal **S**tudy of **A**dult **M**en* (**ULSAM**) investigators thank Tomas Axelsson, Ann-Christine Wiman and Caisa Pöntinen for their assistance with genotyping. Genotyping was performed by the SNP Technology Platform in Uppsala (www.genotyping.se). The SNP Technology Platform is supported by Uppsala University and the Knut and Alice Wallenberg Foundation. E.I. was supported by grants from the Swedish Research Council and the Swedish Foundation for Strategic Research.
[representing authors: UR, PS, EI]

The ***G**ene-**L**ifestyle interactions **A**nd **C**omplex traits **I**nvolved in **E**levated disease **R**isk* (**GLACIER**) study is nested within the Northern Swedish Health and Disease Study cohort and the Västerbotten Intervention Programme (VIP). We are indebted to the study participants who dedicated their time and samples to these studies. We also thank the VIP and Umeå Medical Biobank staff for biomedical data collection and preparation. We specifically thank John Hutiainen, Åsa Ågren and Sara Nilsson (Umeå Medical Biobank) for data organization, Kerstin Enquist and Thore Johansson (Västerbottens County Council) for expert technical assistance with DNA preparation, and David Hunter, Patrice Soule and Hardeep Ranu (Harvard School of Public Health) for expert assistance with planning and undertaking genotyping of GLACIER samples. The GLACIER Study was funded by project grants from Novo Nordisk (P.W.F.), the Swedish Heart-Lung Foundation (P.W.F.), the Swedish Diabetes Association (to P.W.F.), Påhlssons Foundation (P.W.F), the Swedish Research Council (P.W.F.), Umeå University Career Development Award (P.W.F), and The Heart Foundation of Northern Sweden (P.W.F). F.R. was supported by a post-doctoral stipend from the Swedish Heart-Lung Foundation.
[representing authors: GH, FBH, IJ, FR, OR, PWF]

The generation and management of GWAS genotype data for the ***Rotterdam** Study* is supported by the Netherlands Organization of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012), the Research Institute for Diseases in the Elderly (014-93-015; RIDE2),EUROSPAN (European Special Populations Research Network;LSHG-CT-2006-01947),the Netherlands Organization for Scientific Research (Pionier, 047.016.009, 047.017.043;050-060-810), Erasmus Medical Center and the Centre for Medical Systems Biology (CMSB I and II and Grand; National Genomics Initiative) of the Netherlands Genomics Initiative (NGI); The Rotterdam Study is further funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. We thank Pascal Arp, Mila Jhamai, Dr Michael Moorhouse, Marijn Verkerk, and Sander Bervoets for their help in creating the GWAS database. The authors are grateful to the study participants, the staff from the Rotterdam Study and the participating general practitioners and pharmacists.
[representing authors: FJAvR, EJGS, AGU, AH, CZ, CMvD, JCMW]

***In**vecchiare in **Chianti** (aging in the Chianti area,* **InCHIANTI**) study investigators thank the Intramural Research Program of the NIH, National Institute on Aging who are responsible for the InCHIANTI samples. Investigators also thank the InCHIANTI participants. The InCHIANTI study baseline (1998-2000) was supported as a “targeted project” (ICS110.1/RF97.71) by the Italian Ministry of Health and in part by the U.S. National Institute on Aging (Contracts: 263 MD 9164 and 263 MD 821336).
[representing authors: TT, SB, LF]

The ***Gen**e-**D**iet **A**ttica **I**nvestigation on childhood obesity* (**GENDAI**) and The ***G**reek **H**ealth **R**andomized **A**ging **S**tudy* (**GHRAS**) would like to thank all the field investigators for samples and data collection and all the children, their parents and the elderly people for participation in the studies. The GENDAI cohort was supported by a research grant from Coca Cola Hellas.
[representing authors: SK, CP, AJB, CJG, IP, GD]

Table S1. Participating cohorts

Cohort	Study description [1]	Web Link and Relevant Reference
Health, Aging and Body Composition (Health ABC). **USA**	The Health ABC study is a prospective cohort study investigating the associations between body composition, weight-related health conditions, and incident functional limitation in older adults. Health ABC enrolled well-functioning, community-dwelling black (n=1281) and white (n=1794) men and women aged 70-79 years between April 1997 and June 1998. Participants were recruited from a random sample of white and all black Medicare eligible residents in the Pittsburgh, PA, and Memphis, TN, metropolitan areas. Participants have undergone annual exams and semi-annual phone interviews. A total of 1,249 Caucasian participants who attended the second exam in 1998-1999, and who had available genotyping and food frequency data were eligible for the current study.	http://www.nia.nih.gov/ResearchInformation/ScientificResources/HealthABCDescription.htm
Cardiovascular Health Study (CHS) **USA**	The CHS is a prospective population-based cohort study of people ≥ 65 years old at baseline initiated to evaluate risk factors for the development and progression of cardiovascular disease. Participants were recruited at four field centers (Forsyth County, NC; Sacramento County, CA; Washington County, MD; Pittsburgh, PA)]. The baseline exam was conducted in 1989-1990. Overall, 5,201 individuals were recruited from random samples of Medicare eligibility lists. A total of 2,765 adults with available DNA, valid dietary information, and consent to share genetic data were eligible for the current analysis.	http://www.chs-nhlbi.org/ Ann Epidemiol. 1(3): 263-276, 1991 (1)
Framingham Heart Study (FHS) **USA**	The Framingham Offspring Study is a community-based longitudinal study designed to examine CVD risk in the offspring of the original participants and their spouses of the Framingham Heart Study cohort. In 1971, 5,124 individuals were enrolled in the study; since then, the cohort has been examined every 3–4 y. Between 1991 and 1995, during the 5th examination cycle, 3,799 adults, with a mean age of 54.98, underwent a standardized medical history and physical examination. Beginning in 2002, 4,095 Gen III participants, who had at least one parent in the offspring cohort, were enrolled in the Framingham Heart Study. At the first cycle of the Gen III study, 4,095 individuals with a mean age of 40 y, underwent the standard clinic examination. For the present study both cohorts were combined for the analysis. A total of 5,835 adults with available DNA, valid dietary information, and consent to share genetic data were eligible for the current study.	http://www.framinghamheartstudy.org/ Prev Med.4:518–25, 1975 (2) Am J Epidemiol. 165(11):1328-35, 2007 (3)
Atherosclerosis Risk in Communities (ARIC) **USA**	The ARIC study is a population-based cohort study designed to study of new and established risk factors for atherosclerosis and community trends in coronary heart disease. In 1987-89, baseline data was collected on 15,792 adults, aged 45–64 y, living in four U.S. communities (Forsyth County, NC; Jackson, MI; northwest Minneapolis suburbs, MN; Washington County, MD). The baseline exam was conducted in 1987-89 and information was collected on African Americans, Whites, and a few adults of other ethnicities, aged 45–64 y. After providing informed consent, 15,792 adults were enrolled (8,710 women and 7,082 men). A total of 7,201, Caucasian adults with available DNA, valid dietary information, and consent to share genetic data were eligible for the current analysis.	http://www.cscc.unc.edu/aric/ Am J Epidemiol. 129(4): 687-702, 1989 (4)
Family Heart Study (FamHS) **USA**	The FHS began in 1992 with the ascertainment of 1,200 families (50% randomly sampled, and 50% high risk for CHD). The families (~6,000 individuals,) were sampled on the basis of information on probands from four population-based parent studies: the Framingham Heart Study, the Utah Family Tree Study, and two ARIC centers (Minneapolis, and Forsyth County, NC). Approximately eight years later, study participants belonging to the largest pedigrees were invited for a second clinical exam. A total of 2,767 participants of European descent in 510 extended families were examined. A total of 2,094 adults with available DNA and who provided valid dietary information were eligible for the current study.	https://dsgweb.wustl.edu/PROJECTS/MP1.html Higgins et al. Am J Epidemiol. 143 (12): 1219, 1996 (5)

The Age, Gene/Environment Susceptibility -Reykjavik Study (AGES) **Iceland**	The AGES-Reykjavik Study was initiated to examine potential genetic susceptibility and gene/environment interaction as these contribute to disease, disability, and risk of death. AGES-Reykjavik participants are survivors from the Reykjavik Study. The Reykjavik Study, a longitudinal study, began in 1967 and ended in 1994 and recruited over 20,000 participants. Between 2002 and 2006, 5,764 adults with a mean age of 77 years were examined for clinical and subclinical risk factors of vascular, neurocognitive, musculoskeletal, and metabolic diseases of aging. A total of 2,819 adults with available DNA, dietary information, and consent to share genetic data were eligible for the current analysis.	http://www.hjartarannsokn.is/index.aspx?GroupId=346 Harris T, et al. Am J Epidemiol. 165:1076–1087, 2007 (6)
Fenland **UK**	The Fenland study is a cross-sectional study of 5,000 individuals aged 30-55 years in Cambridgeshire, UK. This study was designed to examine the interactions between lifestyle and genetic factors on the risk of obesity and related metabolic traits. Healthy men and women born between 1950 and 1975 and registered at medical practices in Cambridgeshire were eligible to participate in this study. For the present study, 720 adults with available DNA and who provided complete dietary information were eligible for the current study.	http://www.mrc-epid.cam.ac.uk/Studies/Fenland/
Malmö Diet and Cancer (**Malmö**) Study **Sweden**	The Malmö study is a population-based cohort designed to investigate the relationship between dietary factors and certain forms of cancer. At baseline in 1991-1996, a total of 28,449 adults, aged 40 to 70 years were invited to participate in the study. The cardiovascular sub-cohort consists of 6,103 adults (46-68 y, 58% females) randomly selected from the parent Malmö cohort. A total of 4,924 **adults** with available DNA and who provided valid dietary information were eligible for the current analysis.	Berglund, et al. J Intern Med. 233, 45-51, 1993 (7)
Uppsala Longitudinal Study of Adult Men (ULSAM) **Sweden**	The ULSAM is a longitudinal community-based cohort study aimed at identifying metabolic risk factors for CVD and type 2 diabetes. The study was initiated in 1970-74, when all 50-year old men living in Uppsala were invited to enroll in the study and a follow up study was conducted 20 years later. Of the 1,681 available 70-year old men invited to the follow up study, a total of 942 non-diabetic adults with available DNA and data from a seven-day registration were eligible for the current analysis.	http://www.pubcare.uu.se/ULSAM/ Ingelsson E, et al. JAMA. 294(3):334-341, 2005 (8)
Gene-Lifestyle interactions And Complex traits Involved in Elevated disease Risk (GLACIER) **Sweden**	The GLACIER Study is a population-based cohort study of ~20,000 adults in the northern Swedish county of Västerbotten. As part of the Västerbotten Intervention Programme (VIP), a health and lifestyle examination was conducted on the majority of GLACIER participants. VIP is an ongoing population-wide project aimed at monitoring the health of Västerbotten residents and providing information on healthful lifestyle behaviors to study participants. Since 1985, all residents of the county of Västerbotten, aged 40-60 years, have been invited to visit their primary health care centre for clinical examinations. For the present study, non-diabetic adults with available DNA, valid dietary information, and consent to share genetic data were eligible for the current analysis (891 samples for insulin analyses; up to 14,913 for glucose analyses).	Renström F, et al. Hum Mol Genet. 18(8):1489-96, 2009 (9) Hallmans G, et al. Scand J Public Health Suppl.61:18-24, 2003 (10)

Rotterdam Study **Netherlands**	The Rotterdam Study is a prospective population-based cohort study designed to investigate the prevalence and incidence of and risk factors for chronic diseases in the elderly. The baseline exam was conducted between 1990 and 1993 in Ommoord, a suburb of Rotterdam. A total of 7,983 adults, aged 55 years and over, participated in the study. A total of 2,304 adults with available DNA, valid dietary information, and consent to share genetic data were eligible for the current analysis.	http://www.epib.nl/research/ergo.htm Hofman A, et al. Eur J Epidemiol. 24(9):553-572, 2009 (11)
Invecchiare in Chianti (aging in the Chianti area, InCHIANTI) **Italy**	InCHIANTI is a population-based study designed to evaluate the factors that influence mobility in older people in the Chianti region of Tuscany, Italy. A total of 1,616 residents were selected from the population registry of Greve (a rural area: 11,709 residents with 19.3% of the population greater than 65 years of age), and Bagno a Ripoli (Antella village near Florence; 4,704 inhabitants, with 20.3% greater than 65 years of age). The participation rate was 90% (n=1453), and the participants ranged between 21-102 years of age. For the present study, 1,071 adults with available DNA and who provided complete dietary information were eligible for the current study.	http://www.inchiantistudy.net/bindex.html Ferrucci L, et al. J Am Geriatr Soc. 48:1618-1625, 2000 (12)
Gene-Diet Attica Investigation on Childhood Obesity (GENDAI) **Greece**	The GENDAI study examines the contribution of genetics and nutrition, and the potential interactions between them, to childhood obesity. Between November 2005 and June 2006, 900-1000 registered fifth- and sixth-grade children, from 40 primary schools in the Attica region of Greece, were enrolled in this study. Parents or guardians of interested students signed a written informed consent form and participating children provided verbal assent. For the present study, only 1,087 children with available DNA, valid dietary information, and consent to share genetic data were eligible for the current analysis.	Papoutsakis et al. Clin Chem Lab Med. 45(3): 039-315, 2007 (13)
Greek Health Randomized Aging Study (GHRAS) **Greece**	GHRAS is a cross-sectional health and nutrition study conducted in elderly (≥60 y) urban Greek adults. Between 2004 and 2008, a randomly selected group of 800 adults, who were members of the "Centers of Open Protection for the Elderly" in the Athens region, were selected to participate. The Centers of Open Protection for the Elderly is a public entity that provides assistance from social workers, first-degree medical care, and recreational activities for the elderly. A total of 865 adults with available DNA, valid dietary information, and consent to share genetic data were eligible for the current analysis.	Kanoni & Dedoussis. Med Sci Monit 2008; 14(4): CR204-212 (14)

[1] All protocols were approved by each field center's institutional review board. Study participants were of European descent. Exclusion criteria included prevalent diabetes. Validity of dietary data was determined differently by each cohort.

Table S2. Characterization of whole grain intake in each of 14 cohorts

	Dietary Assessment Method	Description	FFQ Line items / Top contributing Food Groups
Health ABC	FFQ	A 108-item interviewer-administered FFQ (Block Dietary Data Systems, Berkeley, CA). Participants were asked to indicate how often, on average, they consumed various foods and beverages over the past year according to nine frequency categories, ranging from "never" to "every day". Portion size information was collected by trained interviewers using wood blocks, food models, standard kitchen measures, and flash cards to help participants estimate portion sizes. Individuals with serious errors (skipped >15% of items or reported <3 or >20 foods/day) on the FFQ and those who reported energy intakes less than 500 kcal/d or greater than 3,500 kcal/d in women and less than 800 kcal/d or greater than 4,000 kcal/d in men were excluded. **Related References**: Houston et al. Am J Clin Nutr. 2008; 87(1):150-5. (15)	**Three Line Items:** Whole wheat, rye or other dark breads High-fiber cold cereal Cooked cereal
CHS	FFQ	Usual dietary intake was assessed using a picture-sort version of the National Cancer Institute FFQ. This is a 99-item, self-administered FFQ. Participants were asked to indicate how often, on average, they consumed various foods and beverages over the past year according to 9 frequency categories, ranging from never to ≥5 times per week.. Portion sizes were illustrated by color pictures or laminated 4 X 6 in (10 X 15 cm) index card with a black-and white line drawing. Dietary information was judged as unreliable and excluded from further analysis if calculated total kilocalories were < 500 or > 5000 kcal/d. **Related References**: Kumanyika S, et al. J Am Diet Assoc. 1996 Feb;96(2):137-44. (16)	**Three Line Items:** Whole wheat, rye, or pumpernickel bread Whole grain cold cereal Cooked cereal
FHS	FFQ	A self-administered 126-item FFQ. Participants were asked to indicate how often, on average, they consumed various foods and beverages over the past year according to 9 frequency categories, ranging from never or <1 time/mo to ≥6 times/d. Portion sizes were specified. Separate questions about the use of vitamin and mineral supplements and the type of breakfast cereal most commonly consumed were also included in the FFQ. Dietary information was judged as unreliable and excluded from further analysis if reported energy intakes were < 2.51 MJ/d (600 kcal/d) or > 16.74 MJ/d (4000 kcal/d) for women and > 17.57 MJ/d (4200 kcal/d) for men or if >= 12 food items were left blank. **Related References**: Rimm et al. Am J Epidemiol 1992;135:1114–26, 1127–36. (17) Salvini S et al. Int J Epidemiol 1989;18:858–67. (18)	**Eight Line Items:** Dark bread Cooked oatmeal Whole grain cold cereal Brown rice Bulgur/kasha/couscous Popcorn Added bran Wheat germ
ARIC	FFQ	An interviewer-administered, 66-item semi-quantitative FFQ that was modified from the validated Willett 61-item FFQ (19) (modifications described elsewhere (20)). Participants were asked to indicate how often, on average, they consumed various foods and beverages over the past year according to 9 frequency	**Three Line Items:**

		categories, ranging from never or <1 time/mo to ≥6 times/d. Standard portion sizes given as a reference for intake estimation. Supplementary questions included regarding frequency of fried food consumption and brand name of the breakfast cereal most commonly consumed (open-ended response). Dietary information was judged as unreliable and excluded from further analysis if total energy intake was estimated to be <500 or >3600 kcal for women and <600 or >4200 kcal for men or if 10 or more items of the FFQ were unanswered. **Related References**: Willett WC, et al. Am J Epidemiol. Jul 1985;122(1):51-65. (19) Stevens J et al. Nutrition Research 1996;16: 735-745. (20)	Dark bread Whole grain cold cereal (by self-reported brand name) Cooked cereal
FamHS	FFQ	A 66-item questionnaire modified from the Willet FFQ administered by trained interviewers. Participants were asked to indicate how often, on average, they consumed various foods and beverages over the past year according to 9 frequency categories, ranging from never or <1 time/mo to ≥6 times/d. Portion sizes were specified. Dietary information was judged as unreliable and excluded from further analysis if reported energy intakes were <3347.2kJ/day (799.3 kcal/day) or >17572.8 kJ/day (4196.4 kcal/day) for men and <2510.4 kJ/d (599.5 kcal/day) or >14644 kJ/day (3497 kcal/day) for women. **Related References**: Stein AD et al. Am J Epidemiol 1992;135(6):667-677. (21) Willett WC, et al. Am J Epidemiol. Jul 1985;122(1):51-65. (19)	**Three Line Items:** Dark bread Whole grain cold cereal (by self-reported brand name) Cooked cereal
AGES	Dietary Questionnaire	A self-administered 30-item dietary practice questionnaire was reviewed by a trained interviewer. Specific questionnaire items were customized to capture food consumption of unique Icelandic foods. Participants were asked to report how often, on average, they consumed various Icelandic foods in a typical week according to seven frequency categories, ranging from never to more than once per day. Portion sizes were not specified.	**Three Line Items:** Rye bread Whole wheat or coarse-grain bread Oatmeal or muesli
Fenland	FFQ	A self-administered 130-item semi-quantitative Willett FFQ. The lists of foods were modified to reflect important sources of nutrients in the average British diet. Food and macronutrient intakes were estimated in grams per day. Participants were asked to indicate how often, on average, they consumed various foods and beverages over the past year according to 9 frequency categories, ranging from never or <1 time/mo to ≥6 times/d. Portion sizes were specified.	**Five Line Items:** Wholemeal bread Porridge/readybrek Whole grain cold cereal Brown rice Wholemeal pasta
Malmö	Modified diet	Participants visited the study centre on two occasions. During the first visit, trained staff gave detailed instructions about the dietary data collection procedure, and distributed the dietary questionnaire and	Whole grain products were originally defined from the modified diet history

	history with FFQ	menu book. At the second visit (after approximately 2 weeks) individual interviews were conducted by trained diet interviewers to complete the diet history and to check for completed questionnaire. The 7 day menu book collected information on cooked lunch and dinner meals, cold beverages, and supplements. The 168-item dietary questionnaire covered foods regularly consumed during past year. Usual portion sizes were estimated using a booklet containing 48 photographs. During the 1-h interview, the participants were asked questions about food choices, portion sizes (using a more extensive book of photos) and food preparation practices. Overlapping information and very high reported intakes were also checked. Regular use of supplements was recorded in a questionnaire. The average daily intake of foods (grams per day) was calculated based on the information available in the menu book (and interview) and questionnaire. Food intake was converted to nutrient intake using a database specifically developed for the Malmö study and originated from the Swedish National Food Administration. Dietary information was judged reliable by a trained interviewer during the 1-hour diet interview. **Related References**: Elmstahl et al. Eur J Clin Nutr 1996; 50:134-42. (22) Elmstahl et al. Eur J Clin Nutr 1996; 50:143-51. (23) Riboli et al. Int J Epidemiol 1997; 26 Suppl 1: S161-73. (24) Callmer et al. J Intern Med 1993; 233,53-7. (25)	which included 23 items for cereals, 7 for bread and 14 for crisp bread. Items were grouped together according to assumed fiber content for inclusion on the FFQ **Three Line Items:** Bread with >6% fiber Grain crisps with >10% fiber Cereals with more than 10% fiber
ULSAM	7-day food record	A 7-day food record, using an optically readable form (OMR) in a subset of 1,138 men. The participants were given oral instructions by a dietitian on how to perform the dietary registration. Each subject recorded their dietary intake in the OMR book, by marking a horizontal pencil stroke in an oval. The menu book included written instructions with an example of how to complete the book. The record sheets started with "day 1" followed by six additional days. For each meal (breakfast, lunch, dinner and snacks) the respondent was asked to specify where and at what time the meal was eaten. The amounts consumed were reported in household measurements or specified as portion sizes according to a photograph showing four different portion sizes. Food items that were eaten, but not described in the menu book, were to be reported as "others". For food not found as a pre-coded alternative and for snacks, some additional coding by a dietitian was needed prior to data input. Dietary information was judged as unreliable and excluded from further analysis if total energy intake was +/- 3SD from the mean energy intake. **Related References**: Becker W, Lennernäs MM, Gustafsson I-B et al. Food intake. The Sixth Nordic Conference in Nutrition. Göteborg, Sweden, 1996	**Top-contributing foods:** Whole grain bread Hot Cereals (mainly porridge)
GLACIER	FFQ	Using a 66-item, self administered FFQ, participants were asked to indicate how often, on average, they consumed various foods and beverages over the past year according to 9 frequency categories, ranging from never to 4 or more a day. Participants indicated their average portion of (1) potato/pasta/rice, (2) vegetables and (3) meat/ground meat/sausages by comparison with four colour photos illustrating four plates with increasing portion sizes of potato, vegetables and meat. For the other food items, we assumed a standard portion size value (as described by the National Food administration's statistics database, www.slv.se). Dietary information was judged as unreliable and excluded from further analysis if estimated energy intake was <2.5% or >95% for the entire Northern Sweden FFQ database (N~93,000 observations). Energy intake values were calculated as estimated energy intake divided by estimated basal metabolic (using the equations defined by Schofield, 1985). **Related References**: Johansson I et al, Public Health Nutr, 2002; 5(3):487-496. (26) Johansson G, et al, Public Health Nutr, 2001; 4(4): 919-927. (27)	**Four Line Items:** Whole grain coarse bread Rye crisp bread High-fiber cold cereals Porridge oat, graham, rye, barley

		Wennberg M, et al. Public Health Nutr. 2009; 12(9): 1477-1484. (28)	
Rotterdam Study	FFQ	Dietary assessment followed a two-step procedure: 1) A simple self-administered questionnaire was first completed at home, only questions were asked about which food items were consumed; no questions about portion sizes (or frequency) were asked during this step. 2) A subsequent structured interview was later conducted at the research center with a trained dietitian Participants were asked to indicate how often, on average, they consumed various foods and beverages over the past year according to 9 frequency categories, ranging from never or <1 time/mo to ≥6 times/d. Portion sizes were presented in natural units (eg. slices of bread) or household measures (e.g., cups, bowls, tablespoons, plates, etc.) Nutritional supplement intakes were not considered because dose and duration were not recorded with sufficient accuracy. Dietary information was judged as unreliable and excluded from further analysis if a dietician considered the reported dietary intake unreliable, i.e. because participant's answers during the dietary interview were either too inconsistent or too incomplete. **Related References**: Klipstein-Grobusch K, et al. Eur J Clin Nutr. 1998 Aug; 52(8):588-96. (29)	**Eight Line Items:** Wheat bread Rye bread Wholemeal bread Porridge oatmeal Muesli Brown rice, boiled Wheat germ Wheat bran
InCHIANTI	FFQ	A 236 item, interviewer administered FFQ that investigates how frequently (weekly, monthly, yearly) each specific food was generally consumed. Participant is asked to specify the size of the portion usually consumed, in comparison to a range of portion that are shown in colored photographs. Nutrient data for specific foods were obtained from the Food Composition Database for Epidemiological Studies in Italy (18). Dietary information was judged as unreliable and excluded from further analysis if reported energy intakes less than 600 kcal/d or greater than 4,000 kcal/d and 4,200 kcal/d in women and men, respectively. **Related References**: Bartali et al. Arch. Gerontol Geriatr. Geriatr. 38 2004; 51–60. (30) Pisani et al. Int J Epidemiol. 1997; 26:152–160. (31)	**One Line Item:** Whole grain bread
GENDAI	24-h recalls	Two 24-h recalls on non consecutive days. The second recall was conducted 3–10 days after the first recall and on a different day of the week. A standardized protocol describing interviewing and recording techniques was implemented during the 24-h recalls to enhance accuracy and completeness. Food models and sample measures (such as cups and spoons) were used to specify serving sizes. The consumption of vitamin and mineral supplements was recorded. The 24-h recall data were analyzed using Nutritionist Pro software, version 2.2 (Axxya Systems-Nutritionist Pro, Stafford,TX, USA). The Nutritionist Pro food database	**Top-contributing foods:** Whole wheat or rye bread Whole wheat or rye melba toast

		was expanded by adding analyses of traditional Greek foods and recipes, and nutrient information for local processed food items (mainly snack foods, sweets, and fast foods) as shared by industry. Dietary information was judged as unreliable and excluded from further analysis if total energy intake was +/- 3SD from the mean energy intake.	Whole wheat or barley rusk High-fiber cold cereal Whole wheat pasta Brown rice Whole wheat crackers
GHRAS	FFQ	A 55-item, interviewer administered FFQ Participants were asked to indicate how often, on average, they consumed various foods and beverages over the past year according daily, weekly, or monthly. Portion size was specified (1 slice). Dietary information was judged as unreliable and excluded from further analysis if total energy intake was +/- 3SD.	**<u>One Line Item:</u>** Whole wheat bread

Table S3. Genotyping

COHORT	Genotyping platform	Imputed genotypes (yes/no)	Imputation method	Quality control and other procedural details
Health ABC	Illumina Human1M-Duo BeadChip	11 SNPs were imputed: *rs11708067*, *rs11920090*, *rs2191349*, *rs7034200*, *rs10885122*, *rs4506565*, *rs11605924*, *rs7944584*, *rs174550*, *rs10830963*, *rs1107165* 6 SNPs were directly genotyped: *rs340874*, *rs780094*, *rs560887*, *rs4607517*, *rs11558471*, *rs35767*	MACH	Genotyping was performed by the Center for Inherited Disease Research (CIDR) using the Illumina Human1M-Duo BeadChip system. Samples were excluded from the dataset for the reasons of sample failure, genotypic sex mismatch, and first-degree relative of an included individual based on genotype data. Genotyping was successful in 1663 participants of European descent. Analysis was restricted to SNPs with minor allele frequency ≥ 1%, call rate ≥97% and HWE $p \geq 10^{-6}$. Genotypes were available on 914,263 high quality SNPs for imputation based on the HapMap CEU (release 22, build 36) using the MACH software (version 1.0.16).
CHS	Illumina HumanCNV370-Duo BeadChip	12 imputed; not imputed = rs340874, rs4607517, rs560887, rs780094	BIMBAM10 v0.91	CHS study samples were genotyped using the Illumina HumanCNV370-Duo BeadChip system. African American participants were excluded from analyses. Genotyping was successful in 3,291 participants of European descent free of cardiovascular disease at baseline. The following exclusions were applied to identify a final set of 332,946 SNPs: call rate >95%, HWE $P > 10^{-5}$, 2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios). Imputation was performed using BIMBAM10 v0.91 with reference to HapMap CEU using release 21A, build 35 using one round of imputations and the default expectation-maximization warm-ups and runs. SNPs were excluded for variance on the allele dosage ≤0.01.
FHS	Affymetrix 500K and MIPS 50K	Yes	MACH	FHS study samples were genotyped using Affymetrix 500K (250K Nsp and 250K Sty) and MIPS 50K. Samples QC: call rate filter was set at > 97%; heterozygosity filter was set at 5 SD from the mean; samples were excluded if > 1000 Mendelian errors. SNPs QC: MAF >1%; HWE $< 10^{-6}$; call rate > 95%. Imputation was made using MACH software: Ratio of variance of dosage to expected variance under binomial model >0.3.

ARIC	Affymetrix 6.0	Yes	MACH	ARIC Study samples were genotyped using the Affymetrix Genome-Wide Human SNP Array 6.0 (Santa Clara, California); for the current analysis only white participants were analyzed. Sample exclusion criteria included discordant with previous genotype data, genotypic and phenotypic sex mismatch, suspected first-degree relative of an included individual based on genotype data, genetic outlier as assessed by Identity by State (IBS) using PLINK and >8 SD along any of the first 10 principal components in EIGENSTRAT with 5 iterations. Autosomal SNPs were used for imputation after exclusion of SNPs with HWE deviation $p<5 \times 10^{-5}$, call rate <95%, or MAF<1%.
FamHS	Illumina HumMap chip (974 on 550K, 249 on 610K, and 1482 on 1Million)	Yes	MACH	All participants were typed on an Illumina HumMap chip. The initial 974 were typed with 550K density; 249 were typed at 610K, and the remaining 1482 at 1M. Of these, 34 (3.3%) were excluded due to technical errors, call rates below 98%, and discrepancies between reported sex and sex-diagnostic markers. There was no significant plate-to-plate variation in allele frequencies.
AGES	Illumina 370CNV BeadChip array	Yes	MACH	Genotyping was performed using the Illumina 370CNV BeadChip array on 3,664 participants. Sample exclusion criteria included sample failure, genotype mismatch with reference panel, and sex mismatch, resulting in clean genotype data on 3,219 participants. Standard protocols for working with Illumina data were followed with clustering score greater than 0.4. From a total of 353,202 SNPS, 325,094 were used for imputation after exclusion of SNPs with call rate <97%, HWE deviation $<1 \times 10^{-6}$, mishap (PLINK haplotype-based test for non-random missing genotype data [2]) $p<1 \times 10^{-9}$, and mismatched positions between Illumina, dbSNP and/or HapMap.
Fenland	Affymetrix using the BRLMM calling algorithm	15 imputed; not imputed = rs4506565	IMPUTE	All samples were genotyped using the Affymetrix 500K array set. Samples QC: call rate filter was set at > 95% with 1 individual excluded; heterozygosity uperband 0.28822 lowerband 0.27348, 81 participants were excluded. SNPs QC: MAF >1%; HWE $< 10^{-6}$. Imputation was made using IMPUTE (v0.4.2) with MAF set at >1%
Malmö	Sequenom (GCK, FADS1, TCF7L2) Taqman (GCKR)	No	NA	The SNPs were genotyped using either the iPLEX Sequenom MassARRAY platform (GCK, TCF7L2, FADS1) or allelic discrimination (GCKR) on an ABI 7900 instrument (Applied Biosystems). All genotyped SNPs had a genotyping call rate >95% (mean 97.8%) and a Hardy-Weinberg equilibrium P<0.10.
ULSAM	SNPstream GetGenos (Beckman Coulter)	No	NA	The SNPs were genotyped by multiplex minisequencing (fluorescent single base extension) using the SNPstream system (Beckman Coulter) (Ref: Bell PA, Chaturvedi S, Gelfand CA, Huang CY, Kochersperger M, Kopla R, Modica F, Pohl M, Varde S, Zhao R, Zhao X, Boyce-Jacino MT. SNPstream UHT: ultra-high throughput SNP genotyping for pharmacogenomics and drug discovery. Biotechniques. 2002; 30:S70-77). SNP QC filters: MAF>5%; HWE$<10^{-3}$; Call rate>93%. Average SNP call rate: 0.97777335625. Sample QC filters: Call rate>95%. Average sample call rate: 0.97629158
GLACIER	OpenArray SNP Genotyping System (BioTrove, Woburn, MA, U.S.A)	No	N/A	All participants were of Northern European ancestry (white Swedish). DNA was extracted at the Medical Biobank in Umeå from peripheral white blood cells. Genomic DNA samples were subsequently diluted to 4 ng/µl. Genotyping was undertaken at the Wellcome Trust Sanger Institute (Hinxton, UK) using OpenArray SNP Genotyping System (BioTrove, Woburn, MA, U.S.A), in accordance with the recommended protocols. Approximately 10% duplicate samples were included for the assessment of genotyping concordance. The mean concordance was 99.3% and the mean success rate was 98.4%

Rotterdam	Illumina 550K	Yes	MACH	Genotyping was conducted using the Illumina 550K array among participants of self-reported European descent, and succeeded in 6,240 participants (sample call rate = 97.5%). We excluded participants for excess autosomal heterozygosity, mismatch between called and phenotypic gender, or being outliers identified by the IBS clustering analysis. The final population for genetic analysis comprised 5,974 participants. SNPs were excluded for minor allele frequency <1% , Hardy-Weinberg equilibrium p-value<10^{-6}, or SNP call rate <90% resulting in data on 530683 SNPs.
InCHIANTI	Illumina 550K	Yes	MACH	Genotyping in InCHIANTI was conducted using Illumina 550K. Samples QC: call rate filter was set at > 98.5%; sex misspecification. SNPs QC: MAF >1%; HWE > 10^{-4}; call rate > 99%. Imputation was made using MACH software: Ratio of variance of dosage to expected variance under binomial model >0.3, MAF > 1%.
GENDAI	Applied Biosystems Taqman	No	N/A	Genotyping was performed using Taqman (Applied Biosystems), in accordance with the recommended protocols. The mean call rate for all SNPs was >95%
GHRAS	Applied Biosystems Taqman	No	N/A	Genotyping was performed using Taqman (Applied Biosystems), in accordance with the recommended protocols. The mean call rate for all SNPs was >95%

Table S4. Effect allele frequencies for investigated SNPs in each of 14 cohorts

Nearest Gene	*SNP*	Risk-raising allele[1]	Health ABC	CHS	FHS	ARIC	FamHS	AGES	Fenland	Malmö	ULSAM	GLACIER	Rotter-dam	InCHIANTI	GENDAI	GHRAS
PROX1	rs340874	C	0.535	0.527	0.528	0.532	0.573	0.569	0.556	NA	0.525	0.529	0.568	0.535	0.508	0.518
GCKR	rs780094	C	0.603	0.573	0.554	0.602	0.594	0.648	0.628	0.650	0.659	0.715	0.634	0.470	0.522	0.540
G6PC2	rs560887	C	0.708	0.712	0.703	0.704	0.692	0.692	0.713	NA	0.664	0.709	0.684	0.710	0.715	0.708
ADCY5	rs11708067	A	0.777	0.782	0.791	0.774	0.780	0.788	0.764	NA	0.779	0.794	0.730	0.848	0.842[2]	0.803[2]
SLC2A2	rs11920090	T	0.867	0.862	0.867	0.866	0.865	0.896	0.873	NA	0.872	0.860	0.868	0.845	0.834	0.837
DGKB/TMEM195	rs2191349	T	0.543	0.549	0.557	0.536	0.540	0.509	0.551	NA	0.498	0.492	0.537	0.571	0.554	0.558
GCK	rs4607517	A	0.159	0.185	0.181	0.170	0.161	0.130	0.178	0.150[6]	0.148	0.151	0.182	0.199	0.179	0.195
SLC30A8	rs11558471	A	0.709	0.677	0.736	0.682	0.680	0.649	0.713	NA	NA	0.704[4]	0.703	0.729	NA	NA
GLIS3	rs7034200	A	0.485	0.494	0.490	0.487	0.465	0.489	0.485	NA	0.466	0.570	0.486	0.506	0.522	0.518
ADRA2A	rs10885122	G	0.888	0.896	0.891	0.881	0.899	0.890	0.888	NA	0.879	0.885	0.888	0.874	0.875	0.884
TCF7L2	rs4506565	T	0.315	0.310	0.328	0.310	0.311	0.306	0.314	0.260[5]	0.262[5]	0.205[5]	0.291	0.362	NA	NA
CRY2	rs11605924	A	0.465	0.446	0.461	0.470	0.469	0.500	0.519	NA	0.493	0.504	0.482	0.464	0.449	0.415
MADD	rs7944584	A	0.716	0.723	0.703	0.729	0.716	0.755	0.729	NA	0.758	0.757	0.709	0.634	0.700	0.642
FADS1	rs174550	T	0.677	0.677	0.673	0.667	0.674	0.603	0.676	0.690[7]	0.646	0.659	0.665	0.720	0.707	0.729
MTNR1B	rs10830963	G	0.278	0.290	0.279	0.277	0.292	0.260	0.285	NA	0.256	0.280	0.253	0.235	0.283	0.264
C2CD4B	rs11071657	A	0.642	0.630	0.635	0.626	0.611	0.590	0.634	NA	0.657	0.598	0.637	0.642	0.666[3]	0.683[3]
IGF1	rs35767	G	0.829	0.853	0.844	0.848	0.837	0.866	0.855	NA	0.849	0.850	0.842	0.819	0.803	0.772

[1]Risk-raising allele = allele positively associated with elevated fasting glucose or fasting insulin in MAGIC consortia (32)

[2]Proxy SNP used: *rs11717195*

[3]Proxy SNP used: *rs12440695*

[4]Proxy SNP used: *rs13266634*

[5]Proxy SNP used: *rs7903146*

[6]Proxy SNP used: *rs17998846*

[7]Proxy SNP used: *rs174548*

Table S5. Methods: fasting glucose and insulin quantification and assessment other relevant participant characteristics[1]

COHORT	Fasting glucose quantification [1]	Fasting insulin quantification [1]	Assessment of other relevant participant characteristics [2]
Health ABC	≥8-hour fasting plasma glucose was measured by an automated glucose oxidase reaction (YSI 2300, Yellow Springs, OH).	≥8-hour fasting plasma insulin was assayed with a microparticle enzyme immunoassay (Abbott IMx).	Demographic and socioeconomic characteristics were ascertained by questionnaire at baseline. BMI was calculated using measured weight (kg, year 2 visit when FFQ data ascertained) and height (m^2, at baseline). Physical Activity: Categorized into minutes of walking per week: (0 mins, >0 and <150 mins/wk, ≥150 mins/wk) Field Center: 2 centers Level of Education: Categorized in 3 groups: <high school degree, high school degree, postsecondary degree Smoking: Classified as current, former, and never smoking. Alcohol: Categorized into 4 groups: none in past year, <1 drink/week, 1-7 drinks/week, >1 drink/day
CHS	≥8-hour fasting glucose was measured using a Kodak Ektachem 700 analyzer with reagents (Eastman Kodak, Rochester, NY). The overall CV was 1.86%, and the correlation coefficient between 169 pairs of blind replicates was 0.997.	≥8-hour fasting insulin. Fasting insulin was measured by radioimmunoassay (Coat-A-Count Insulin assay (Diagnostics Products Corp, Los Angeles, CA)	Participants completed standard questionnaires on medical history, health status, and personal habits and underwent a clinic examination Body mass index (BMI) was calculated from measured weight (kg)/height $(m)^2$. Physical Activity: Derived from a questionnaire and exercise intensity was classified into 3 categories (none, low/moderate, high) Field Center: 4 centers Level of Education: Categorized in 3 groups: (1) no high school degree, (2) high school or vocational school degree, (3) college degree Smoking: classified as current, former, and never smoking. Alcohol: Calculated as drinks per week
FHS	≥8-hour fasting plasma glucose was measured with a hexokinase reagent kit (A-gent glucose test, Abbott, South Pasadena, California). Glucose assays were run in duplicate, and the intra-assay coefficient of variation ranged from 2% to 3%, depending on the assayed glucose level	≥8-hour fasting insulin concentrations were measured in EDTA plasma as total immunoreactive insulin (Coat-A-Count insulin; Diagnostic Products, Los Angeles, CA) at exam 5 in the Framingham Offspring Cohort and with a human-specific insulin assay (Linco Inc, St Louis, MO) in the Framingham Generation III cohort.	Demographic and socioeconomic characteristics were ascertained at the baseline examination by a trained interviewer. Height (to the nearest 0.25 inch) and weight (to the nearest 0.25 lb) were measured with the subject standing, with shoes off, wearing only a hospital gown. Body mass index (BMI) was calculated from measured weight (kg)/height$(m)^2$. Physical Activity: PAL was assessed as a weighted average of the proportion of a typical day spent sleeping and performing sedentary, slight, moderate, or heavy physical activities (expressed in metabolic equivalents) (33). Family Structure: Unique to Framingham Level of Education: Continuous, ranging from 0 to 30 years of education. Smoking : Classified as cigarettes smoked regularly in last year (yes/no) Alcohol: Calculated as grams per day
ARIC	≥8-hour fasting blood samples were drawn from an antecubital vein into tubes containing a serum separator gel. Serum glucose levels were assessed with a hexokinase/glucose-6-phosphate dehydrogenase method.	≥8-hour fasting insulin was measured by radioimmunoassay (^{125}Insulin kit; Cambridge Medical Diagnosis, Bilerica, MA), with a 7 pmol/l lower limit of sensitivity and 33% cross-reactivity with proinsulin (34)	Demographic and socioeconomic characteristics were ascertained at the baseline examination by a trained interviewer. Height (to the nearest 1 cm) and weight (to the nearest 0.50 lb) were measured with the subject standing, with shoes off, wearing light-weight, non-restrictive underwear. Body mass index (BMI) was calculated from measured weight (kg)/height$(m)^2$. Physical Activity: Assessed as both sport and leisure time using the Baecke questionnaire (35). A sports activity score and a leisure activity score ranged from low to high (five quintile categories)

			Field Center: 4 centers Level of Education: Categorized in the following 6 groups: (grade school or none, some high school, high school graduate, vocational school, college, graduate/professional school). Smoking: Current/ former/ never/ missing or unknown Alcohol: Calculated as grams per day
FamHS	≥8-hour fasting blood samples were collected, allowed to clot, centrifuged, aliquoted, and frozen at -70 degrees Celsius before shipment to a central processing laboratory. At the central processing laboratory, glucose was measured by a thin film adaptation of a glucose oxidase enzymatic, spectrophotometric procedure using the Vitros analyzer (Ortho Clinical Diagnostics, Rochester, NY)	≥8-hour fasting insulin was measured using the coated-tube radioimmunoassay method distributed by Diagnostic Products Corp. (Los Angeles, CA)	Demographic and socioeconomic characteristics were ascertained at baseline by questionnaire. Body mass index (BMI) was calculated from measured weight (kg)/height(m)^2. Physical Activity: Expressed as minutes per day spent exercising Level of Education: Categorized in 3 groups (high school graduate or less, vocational school, college or more) Field Center: 4 centers and family structure unique to study. Smoking: Classified as current, former, never, missing or unknown. Alcohol: Expressed as drinks per week and expressed as non-drinkers, 1-3 drinks, 4-7 drinks, 8-14 drinks, ≥14 drinks
AGES	≥8-hour fasting blood samples were collected from participants. Glucose was measured on a Hitachi 912 using reagents from Roche Diagnostics following manufacturer's instructions.	Insulin was measured in serum by electrochemiluminescence immunoassay on the Roche Elecsys 1010/2010 analyzer.	Demographic and socioeconomic characteristics were ascertained from self-report through an interviewer-administered questionnaire. BMI was calculated from clinical measurements for height and weight. Physical Activity: Assessed by questionnaire and participants self-reported how often they participated in moderate or vigorous physical activities in current life. Five categories of physical activity: never, rarely, occasionally, moderately often or frequently. Level of Education: Categorized in 4 groups - primary school, secondary school, college, and university. Smoking: Current smokers and not-current smokers (yes/no). Alcohol: Calculated as grams per week
Fenland	≥8-hour fasting plasma glucose was measured with a hexokinase kit (Siemens Healthcare). The assay is automated on the Dimension RxL Analyser (Siemens Healthcare). The absorbance due to NADH is determined using a bichromatic endpoint technique.	For serum insulin, samples are assayed in singleton on a 1235 AutoDELFIA automatic immunoassay system using a two-step time resolved fluorometric assay (Kit No. B080-101). All reagents, standards and consumables are those recommended and supplied by the manufacturer.	Demographic and socioeconomic characteristics were ascertained?? Body mass index (BMI) was calculated from measured weight (kg)/height(m)^2. Physical Activity: Not available Level of Education: Not available Smoking: Current/ former/ never/ missing or unknown Alcohol: Current / former/ never drinker/ missing or unknown
Malmö	Glucose was measured in overnight fasting whole blood samples by a hexokinase-glucose-6-phosphate dehydrogenase method. Blood glucose was converted to plasma glucose using a correction factor of 1.13.	Insulin was measured by non-specific radioimmunassay in overnight fasting blood samples.	Demographic and socioeconomic characteristics were ascertained from an extensive questionnaire. BMI was calculated from measured weight (kg)/height(m)^2. Physical Activity: Leisure-time physical activity was obtained from a list of 18 different activities. The duration of each activity was multiplied by an intensity factor creating a score. The score was divided into quartiles. Level of Education: Categorized in 6 groups: elementary; primary and secondary; upper secondary; further education without a degree; university degree; unknown Smoking: Classified as current, former, never smoking, or missing/unknown

			Alcohol: Non consumers (no alcohol in the 7-day food diary + no alcohol consumption during the previous year in the questionnaire). Other participants were divided into gender-specific quintiles according to their reported intake in the 7-day diary.
ULSAM	≥8-hour fasting venous plasma samples were obtained from the antecubital vein. Glucose was measured by the glucose dehydrogenase method (Gluc-DH, Merck, Darmstadt, Germany). The intra-individual CV for fasting plasma glucose was 3.2%.	Plasma insulin was assayed using an enzymatic-immunological assay (Enzymmun, Boehringer Mannheim, Germany) performed in an ES300 automatic analyser (Boehringer Mannheim) and the levels were originally given in mU/l.	Demographic and socioeconomic characteristics were ascertained at baseline from an extensive interviewer-administered questionnaire. Height was measured to the nearest whole cm, and body weight to the nearest 0.1 kg. BMI was calculated from measured weight (kg)/height(m)^2. Physical Activity: Leisure time physical activity was assessed using a questionnaire and participants were classified into four categories are referred to as sedentary, moderate, regular and athletic physical activity (36). Level of Education: Categorized in 3 groups, elementary school only, secondary school only, college or graduate degree. Smoking: Classified as current (yes/no) Alcohol: Calculated as grams per day
GLACIER	Plasma glucose was assayed using fresh capillary plasma on a benchtop analyser (Reflotron; Boehringer Mannheim, Mannheim, Germany). A threshold glucose value of ≤1 mmol/l was used to exclude potentially spurious values.	Serum insulin was measured on a Roche Modular E170 analyzer, (Roche, Mannheim, Germany) with limits of detection of 2.6-24.9 mIU/L.	Demographic and socioeconomic characteristics were ascertained by the Umeå EPIC lifestyle questionnaire BMI: Height and weight were measured using a calibrated wall-mounted stadiometer and scales, respectively. BMI was calculated as weight in kg/(height in m)^2. Physical Activity: Based on questionnaire response and classified into 5 exercise frequency categories (Never, Infrequently, 1-2 times per week, 2-3 times per week, >3times per week) Level of Education: Categorized into 3 groups- total of 6-7 years of compulsory school education; total 12-13 years of education (school + college); school + college + university Smoking: Classified as current, former, and never smoking. Alcohol: Calculated as grams per day
Rotterdam	≥8-hour fasting blood glucose was measured enzymatically using the Hexokinase method (Boehringer Mannheim).	Fasting blood samples were drawn by venipuncture. Samples were stored at -80 °C. In 2008 insulin levels were measured on a Modular Analytics E170 analyzer, using a Cobas Roche electrochemiluminescence immunoassay (12017547 122).	Demographic and socioeconomic characteristics were ascertained at the baseline examination by a trained interviewer. Height and weight were measured while the participants were wearing indoor clothing and no shoes. Body mass index was expressed in kilograms per square meter. Physical Activity: Expressed as kcal expended per day Level of Education: Categorized in 4 groups: completed primary education, lower vocational training or general education, intermediate vocational training or intermediate and higher general education, and higher vocational training, college, or university. Smoking: Classified as current, former, and never smoking. Alcohol: Calculated as grams per day

InCHIANTI	≥8-hour fasting blood glucose was determined by an enzymatic colorimetric assay using a modified glucose oxidase-peroxidase method (Roche Diagnostics GmbH, Mannheim, Germany) and a Roche-Hitachi 917 analyzer.	Plasma fasting insulin level was determined with a double-antibody, solid-phase radioimmunoassay (intra-assay CV=3.1±0.3%; Sorin Biomedica, Milan, Italy).	Demographic and socioeconomic characteristics were obtained during a structured interview. BMI was calculated from measured weight (kg)/height(m)^2. Physical Activity: The level of physical activity in the 12 months prior the interview was assessed through an modified standard interview-administered questionnaire. Based on the response of 7 questions, PA was collapsed into 3 categories: 1) sedentary (inactivity or light-intensity activity <1 h per week), 2) light physical activity (light intensity activity 2–4 h per week), and 3) moderate-high physical activity (light-intensity activity at least 5 h per week or moderate activity at least 1–2 h per week) Level of Education: Categorized in 3 groups: 1) elementary, secondary, or undocumented, 2) high school or professional school degree, 3) university degree or higher Smoking: Classified as current, former, and never smoking. Alcohol: Calculated as grams per day
GENDAI	≥8-hour fasting blood samples were drawn from an antecubital vein into tubes containing a serum separator gel. Serum glucose levels were assessed using commercially available enzymatic colorimetric assays (Sigma Diagnostics, St. Louis, MO, USA) on an automated ACE analyzer (Schiapparelli Biosystems, Inc., Fairfield, NJ, USA).	Serum insulin was measured via immunofluorescence on an automatic AIA 600II analyzer (Tosoh Corp., Tokyo, Japan) using a commercially available kit for this purpose (ST AIA-PACK IRI, Tosoh Corp.).	Demographic and socioeconomic characteristics were ascertained via an interviewer-administered questionnaire. BMI was calculated from measured weight (kg)/height(m)^2. Physical Activity: Determined from the Sallis physical activity recall checklist and expressed as minutes of physical activity per day Level of Education: Not applicable, all were in 5th or 6th grade of school
GHRAS	≥8-hour fasting blood samples were drawn from an antecubital vein into tubes containing a serum separator gel. Serum glucose levels were assessed using commercially available enzymatic colorimetric assays (Sigma Diagnostics, St. Louis, MO, USA) on an automated ACE analyzer (Schiapparelli Biosystems, Inc., Fairfield, NJ, USA).	Serum insulin was measured via immunofluorescence on an automatic AIA 600II analyzer (Tosoh Corp., Tokyo, Japan) using a commercially available kit for this purpose (ST AIA-PACK IRI, Tosoh Corp.).	Demographic and socioeconomic characteristics were ascertained via an interviewer-administered questionnaire. BMI was calculated from measured weight (kg)/height(m)^2. Physical Activity: Expressed as MET/day Level of Education: Categorized in 4 groups No degree, primary degree, secondary degree, higher degree Smoking: Classified as current, former, and never smoking Alcohol: Calculated as ml per day with a concentration of 12g ethanol/100 ml

[1]Fasting insulin and fasting glucose were quantified from samples collected at the baseline examination (when dietary intake information was collected) in all cohorts, with the exception of Rotterdam, where fasting glucose and fasting insulin were quantified from samples collected approximately 6 years after the assessment of dietary intake.

[2] Table H presents the model covariate defined by cohort

Table S6. Model covariates defined by cohort

Covariates	Health ABC	CHS[1]	FHS	ARIC	FamHS	AGES[2]	Fenland	Malmö	ULSAM	GLACIER	Rotterdam	InCHIANTI	GENDAI	GHRAS
Model 1														
Energy intake (kcal/d)	✓	✓	✓	✓	✓	*NA*	✓	✓	✓	✓	✓	✓	✓	✓
Age (years)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sex (M/F)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Field center or population/family structure*	✓	✓	✓*	✓	✓*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Model 2														
Education[3]	✓	✓	✓	✓	✓	✓	*NA*	✓	✓	✓	✓	✓	*NA*	✓
Smoking History[3] OR Current smoking (yes/no)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	*NA*	✓
Physical activity (PA)[3]	✓	✓	✓	✓	✓	✓	*NA*	✓	✓	✓	✓	✓	✓	✓
Alcohol (ethanol) intake[3]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	*NA*	✓
Model 3														
Fruit *Servings /day or/week* OR*	✓*	✓ w/o fruit juice	✓w/o fruit juice	✓w/o fruit juice	✓w/o fruit juice	✓w/o fruit juice							✓	✓
g/day							✓	✓w/o fruit juice	✓w/o fruit juice	✓	✓	✓ w/o fruit juice		
Vegetables *Servings /day or/week* OR*	✓*	✓No French fries	✓w/o potatoes	✓w/o potatoes	✓w/o potatoes	✓w/o potatoes							✓w/o potatoes	✓w/o potatoes
g/day							✓	✓	✓w/o potatoes	✓	✓	✓w/o potatoes		
Nuts/ seeds *Servings /day or/week* OR*	✓*	✓	✓	✓	✓	*NA*		*NA*					*NA*	*NA*
g/day							✓		✓	✓	✓	✓		
Fish *Servings/day or/week* OR*	✓* w/o seafood	✓	✓ w/o seafood	✓ w/o seafood	✓ w/o seafood	✓							✓	✓
g / day							✓ w/o seafood	✓w/o seafood	✓w/o seafood	✓	✓	✓ w/o seafood		
Coffee (caffeinated; unless otherwise specified) *Servings/day OR*	✓+Decaff	✓ + Decaff	✓	✓	✓									
g/day							✓	✓	✓	✓	✓	✓		

Red or processed meat														
Servings/day or/week OR*	✓*	✓	✓	✓	✓	*not included*[2]							✓	✓
g/day							✓	✓	✓	✓	✓	✓		
Model 4														
BMI (kg/m^2,) continuous	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[1] In CHS, all missing values were imputed.

[2] In AGES, dietary covariates were chosen empirically from the abbreviated list available dietary variables (significant correlation with whole grain intake, p <0.001)

[3] For more details on covariates refer to Table S5

Table S7. Main effects (β ± SE) of daily whole grain servings on fasting glucose and fasting insulin across each of 14 cohorts

Meta-Analyzed Estimate	Health ABC	CHS	FHS	ARIC	FamHS	AGES	Fenland	Malmö	ULSAM	GLACIER	Rotterdam	InCHIANTI	GENDAI	GHRAS
FASTING GLUCOSE (mmol/L)	*n*=1,263	*n*=2,765	*n*=5,835	*n*=7,201	*n*=2,094	*n*=2,748	*n*=720	*n*=4,924	*n*=880-942	*n*=13,242–14,913	*n*=2,304	*n*=1,009-1,071	*n*=1,087	*n*=856
Model 1	-0.079±0.02*	-0.046±0.02*	-0.031±0.005*	-0.017±0.005*	-0.020±0.007*	-0.073±0.01*	-0.010±0.01	-0.012±0.004*	-0.023±0.02	-0.013±0.004*	-0.013±0.007	-0.029 0.03	-0.016±0.02	0.015±0.02
Model 2	-0.076±0.02*	-0.028±0.02	-0.024±0.006*	-0.010±0.005*	-0.013±0.007	-0.074±0.01*	-0.010±0.01	-0.009±0.004*	-0.029±0.02	-0.009±0.004*	-0.009±0.007	-0.025 0.03	-0.017±0.02	0.017±0.02
Model 3	-0.058±0.02*	-0.023±0.02	-0.017±0.006*	-0.011±0.005*	-0.006±0.007	-0.073±0.01*	-0.01±0.01	-0.005±0.004	-0.030±0.02	-0.013±0.004*	-0.003±0.008	-0.024 0.03	-0.018±0.02	0.017±0.02
Model 4	-0.042±0.02	-0.018±0.02	-0.012±0.006*	-0.009±0.005	-0.005±0.007	-0.054±0.01*	-0.004±0.01	-0.004±0.004	-0.021±0.02	-0.011±0.004*	-0.0004±0.007	-0.028 0.03	-0.020±0.02	0.017±0.02
FASTING INSULIN (pmol/L)	*n*=1,249	*n*=2,753	*n*=5,835	*n*=7,201	*n*=2,089	*n*=2,748	*n*=720	*n*=4,765	*n*=872-932	*n*=748-891	*n*=2,240	*n*=983-1,044	*n*=1,064	*n*=670
Model 1	-0.095±0.02*	-0.032±0.01*	-0.016±0.005*	-0.034±0.006*	-0.025±0.008*	-0.084±0.02*	-0.063±0.02*	-0.009±0.004*	-0.038±0.02*	-0.033±0.02	-0.020±0.007*	0.024±0.02	0.035±0.02	-0.025±0.02
Model 2	-0.093±0.02*	-0.034±0.01*	-0.016±0.006*	-0.032±0.006*	-0.025±0.008*	-0.082±0.02*	-0.062±0.02*	-0.010±0.004*	-0.036±0.02*	-0.031±0.02	-0.022±0.007*	0.027±0.02	0.036±0.02	-0.027±0.02
Model 3	-0.071±0.02*	-0.023±0.01	-0.007±0.006	-0.026±0.007*	-0.022±0.008*	-0.077±0.02*	-0.051±0.02*	-0.007±0.004	-0.034±0.02*	-0.028±0.02	-0.017±0.008*	0.027±0.02	0.041±0.02	-0.028±0.02
Model 4	-0.046±0.02*	-0.017±0.01	0.001±0.005	-0.022±0.006*	-0.022±0.007*	-0.031±0.01*	-0.030±0.02*	-0.005±0.004	-0.019±0.02	-0.015±0.02	-0.013±0.007*	0.028±0.02	0.017±0.02	-0.027±0.02

[1]All such values, adjusted for model 1 covariates: sex, age (y), energy intake (kcal/day), [field center in ARIC, CHS, FamHS, Health ABC, InCHIANTI; Principal components were used to adjust for population substructure in FHS and FamHS]

[2]All such values, adjusted for model 2 covariates: above, plus categories of cohort-specific education level metric, categories of cohort-specific physical activity level metric, smoking status (current, former, never), alcohol intake (grams/day)

[3]All such values, adjusted for model 3 covariates: above, plus cohort-defined dietary confounders, including fruit, vegetables, red or processed meats, fish, nuts/seeds, and coffee.

[4]All such values, adjusted for model 4 covariates: above, plus body mass index (kg/m^2)

*p <0.05

Table S8. Interactions between whole grain intake and select SNP genotypes for fasting glucose and fasting insulin across each of 14 cohorts (interaction term β (SE))

Glucose-related SNP	**Health ABC**	**CHS**	**FHS**	**ARIC**	**FamHS**	**AGES**	**Fenland**	**Malmö**	**ULSAM**	**GLACIER**	**Rotterdam**	**InCHIANTI**	**GENDAI**	**GHRAS**
	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)
rs340874	0.009 (0.03)	0.017 (0.02)	-0.009 (0.01)	-0.004 (0.01)	-0.011 (0.01)	0.020 (0.02)	0.002 (0.02)	NA	-0.013 (0.02)	0.004 (0.01)	<0.001 (0.01)	-0.020 (0.03)	0.020 (0.03)	-0.016 (0.03)
rs780094	-0.021 (0.03)	0.018 (0.02)	0.005 (0.01)	-0.005 (0.01)	0.015 (0.01)	-0.018 (0.02)	-0.009 (0.02)	0.004 (0.01)	0.011 (0.02)	0.007 (0.01)	0.003 (0.01)	0.014 (0.04)	0.005 (0.03)	0.040 (0.02)
rs560887	-0.045 (0.04)	-0.002 (0.02)	-0.005 (0.01)	0.006 (0.01)	0.010 (0.01)	-0.026 (0.02)	0.014 (0.02)	NA	0.010 (0.02)	-0.002 (0.002)	-0.009 (0.01)	0.054 (0.04)	0.005 (0.03)	0.026 (0.03)
rs11708067	0.010 (0.04)	0.002 (0.03)	-0.010 (0.01)	0.013 (0.01)	-0.022 (0.01)	0.023 (0.02)	-0.005 (0.02)	NA	0.012 (0.03)	0.009 (0.01)	0.014 (0.01)	-0.058 (0.06)	-0.082 (0.04)*	0.017 (0.03)
rs11920090	0.034 (0.04)	-0.019 (0.03)	0.009 (0.01)	0.003 (0.01)	0.006 (0.01)	0.030 (0.03)	0.004 (0.03)	NA	-0.004 (0.03)	-0.0003 (0.01)	-0.025 (0.01)†	0.006 (0.06)	-0.061 (0.04)†	0.032 (0.03)
rs2191349	-0.009 (0.03)	-0.041 (0.02)†	-0.012 (0.01)†	-0.002 (0.01)	-0.013 (0.01)	0.013 (0.02)	0.081 (0.02)	NA	-0.006 (0.02)	-0.003 (0.01)	0.006 (0.01)	-0.013 (0.04)	-0.015 (0.03)	0.002 (0.03)
rs4607517	0.024 (0.04)	0.016 (0.03)	0.006 (0.01)	0.004 (0.01)	-0.017 (0.01)	0.031 (0.03)	0.013 (0.03)	-0.004 (0.01)	0.023 (0.03)	-0.010 (0.01)	0.014 (0.01)	-0.051 (0.05)	0.003 (0.04)	0.024 (0.03)
rs11558471	-0.025 (0.04)	0.007 (0.02)	-0.027 (0.01)†	0.002 (0.01)	0.006 (0.01)	-0.010 (0.02)	-0.018 (0.03)	NA	NA	-0.001 (0.01)	0.005 (0.01)	0.047 (0.05)	NA	NA
rs7034200	0.013 (0.03)	0.001 (0.02)	0.002 (0.01)	0.005 (0.01)	-0.004 (0.01)	0.014 (0.02)	-0.011 (0.02)	NA	0.025 (0.02)	-0.002 (0.01)	0.014 (0.01)	-0.001 (0.04)	-0.035 (0.03)	-0.023 (0.02)
rs10885122	-0.044 (0.06)	-0.030 (0.04)	0.001 (0.01)	0.009 (0.01)	-0.022 (0.02)	-0.008 (0.03)	0.023 (0.01)	NA	-0.017 (0.03)	0.014 (0.01)	0.013 (0.02)	0.005 (0.06)	0.018 (0.04)	0.036 (0.03)
rs4506565	-0.022 (0.04)	-0.036 (0.02)	-0.008 (0.01)	0.003 (0.01)	0.008 (0.01)	0.008 (0.02)	-0.062 (0.02)*	<0.000 (0.01)	-0.028 (0.03)	0.002 (0.01)	0.026 (0.01)*	-0.041 (0.05)	NA	NA
rs11605924	-0.029 (0.03)	0.014 (0.02)	<0.001 (0.01)	-0.004 (0.01)	<0.001 (0.01)	-0.001 (0.02)	0.015 (0.02)	NA	-0.011 (0.02)	0.009 (0.01)	-0.003 (0.01)	-0.073 (0.04)†	0.059 (0.03)*	0.007 (0.02)
rs7944584	-0.004 (0.04)	0.017 (0.03)	0.009 (0.01)	0.008 (0.01)	0.003 (0.01)	-0.011 (0.02)	0.009 (0.02)	NA	0.004 (0.03)	0.004 (0.01)	-0.002 (0.01)	-0.071 (0.04)†	0.027 (0.03)	0.016 (0.03)
rs174550	-0.001 (0.03)	-0.011 (0.02)	-0.004 (0.01)	-0.012 (0.01)†	-0.003 (0.01)	-0.004 (0.02)	0.035 (0.02)†	-0.010 (0.01)	0.032 (0.02)	0.009 (0.01)	-0.013 (0.01)	0.046 (0.04)	-0.022 (0.03)	-0.047 (0.03)†
rs10830963	-0.034 (0.04)	0.039 (0.03)	-0.001 (0.01)	0.010 (0.01)	-0.001 (0.01)	-0.014 (0.02)	0.067 (0.03)*	NA	-0.040 (0.03)	0.002 (0.01)	0.007 (0.01)	-0.073 (0.05)	0.024 (0.03)	-0.045 (0.03)
rs11071657	-0.025 (0.03)	0.024 (0.02)	0.002 (0.01)	0.003 (0.01)	0.009 (0.01)	0.018 (0.02)	0.017 (0.02)	NA	-0.020 (0.02)	0.004 (0.01)	-0.013 (0.01)	0.046 (0.05)	0.016 (0.03)	0.028 (0.03)
Insulin-related SNP														
rs780094	0.026 (0.03)	-0.009 (0.02)	0.010 (0.01)	-0.012 (0.01)	0.003 (0.01)	-0.010 (0.02)	0.003 (0.03)	0.017 (0.01)	0.023 (0.02)	0.021 (0.02)	0.012 (0.01)	0.035 (0.04)	0.045 (0.03)	0.030 (0.03)
rs35767	-0.046 (0.04)	0.013 (0.03)	0.001 (0.01)	0.002 (0.01)	<0.001 (0.02)	0.015 (0.03)	0.071 (0.04)*	NA	-0.021 (0.03)	-0.040 (0.03)	0.015 (0.01)	0.002 (0.04)	-0.038 (0.04)	0.002 (0.03)

meta-analyzed β (SE) for each interaction are published in main manuscript table
**p <0.05*
† p <0.10

Figure S1. *Relationship between sample size and estimated statistical power for a range of interaction effect sizes.*[1]

[1]Estimations are for an additive genetic model with a per-allele effect size of +0.02 interacting with a continuous environmental exposure with effect size of -0.02 (whole grain and allele effect size estimates selected from published studies (32, 37). (a) estimated power for alpha 0.05; (b) alpha 0.01; (c) alpha 0.001; (d) alpha 0.0001. All power calculations were performed using Quanto version 1.2.3, 2007. Given these sample sizes, previously published reports of effect sizes for each whole grains and the SNPs of interest (32, 37), and our Bonferroni-corrected significance level, we had 80% power to detect interaction regression coefficients ranging from 0.015 to 0.02.

Figure S2. *Mean daily servings of whole grain foods in 14 participating cohorts*[1]

[1]Mean ± SD whole grain foods (servings/day). Values are shown by region in order of ascending intake: North American cohorts = solid black diamonds; Northern European cohorts = solid gray diamonds; Mediterranean European cohorts = open diamonds. All cohorts used food frequency questionnaires; exceptions are starred (*): AGES = specific foods survey; ULSAM = dietary records; GENDAI = 24-hour dietary recalls

Figure S3. *Associations between daily whole grain intake and fasting glucose in 14 cohorts*[1]

[1]Regression coefficient (β (95% CI)) representing expected change in fasting glucose (mmol/L) per 1-daily serving greater whole grain intake

(a) Adjusted for model 2 covariates: sex, age (y), energy intake (kcal/day), [field center in ARIC, CHS, FamHS, Health ABC, InCHIANTI; population substructure by principal components in FHS and FamHS], education level, physical activity, alcohol intake, smoking status.

Education level and physical activity were defined uniquely by cohort; smoking status was characterized as current, former, or never in 12 cohorts and as current or not current in 3 cohorts (FHS, AGES, ULSAM); education level, smoking status, and alcohol intake were not adjusted in the GENDAI cohort (5th and 6th graders).

(b) Adjusted for model 3 covariates: model 2 + red or processed meat, fish, vegetables, fruit, coffee, nuts & seeds

Most cohorts included each of dietary covariates listed in the table as servings per day or grams per day; exceptions are noted in Table S6.

(c) Adjusted for model 4 covariates: model 3 + BMI (kg/m^2)

Figure S4. *Associations between daily whole grain intake and fasting insulin in 14 cohorts*[1]

[1]Regression coefficient (β (95% CI)) representing expected change in fasting insulin ((ln)pmol/L) per 1-daily serving greater whole grain intake

(a) Adjusted for model 2 covariates: sex, age (y), energy intake (kcal/day), [field center in ARIC, CHS, FamHS, Health ABC, InCHIANTI; population substructure by principal components in FHS and FamHS], education level, physical activity, alcohol intake, smoking status.

Education level and physical activity were defined uniquely by cohort; smoking status was characterized as current, former, or never in 12 cohorts and as current or not current in 3 cohorts (FHS, AGES, ULSAM); education level, smoking status, and alcohol intake were not adjusted in the GENDAI cohort (5^{th} and 6^{th} graders).

(b) Adjusted for model 3 covariates: model 2 + red or processed meat, fish, vegetables, fruit, coffee, nuts & seeds

Most cohorts included each of dietary covariates listed in the table as servings per day or grams per day; exceptions are noted in Table S6.

(c) Adjusted for model 4 covariates: model 3 + BMI (kg/m^2)

Figure S5. *Interactions between daily whole grain intake and genotype for select SNPs for fasting glucose in 14 cohorts*[1]

[1]Regression coefficient for interaction between daily servings of whole grains*SNP for fasting glucose (mmol/L), adjusted for age, sex, energy intake and field center (in Health ABC, ARIC, CHS, InCHIANTI) and population structure with principal components in FHS and Fam HS. Interactions with whole grain intake shown for 16 loci: (a) rs340874; (b) rs780094; (c) rs560887; (d) rs11708067; (e) rs11920090; (f) rs2191349; (g) rs4607517; (h) rs11558471; (i) rs7034200; (j) rs10885122; (k) rs4506565; (l) rs11605924; (m) rs7944584; (n) rs10830963; (o) rs174550; (p) rs11071657

Figure S6. *Interactions between daily whole grain intake and genotype for select SNPs for fasting insulin in 14 cohorts*[1]

[1]Regression coefficient for interaction between daily servings of whole grains*SNP for fasting insulin ((ln)pmol/L), adjusted for age, sex, energy intake and field center (in Health ABC, ARIC, CHS, InCHIANTI) and population structure with principal components in FHS and Fam HS. Interactions with whole grain intake shown for 2 loci: (a) rs780094; (b) rs35767

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