Science AMA Series: I'm Ingrid Borecki and I'm a statistical human geneticist who studies heart disease and obesity (with diabetes, lipids, and fatty liver), with a dream of finding new medicines to he

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I've been hearing a lot about high sugar diets being the cause of different conditions like clogged arteries instead of a high fat diet. Is this true?

Also is there a known impact from a high sugar diet on a fatty liver?

slootz

Like just about anything, sugar in moderation is fine, especially if you're active and burning energy on that run or bike ride or whatever. The problem is that most people consume huge amounts of sugar, sometimes hidden in their favorite processed foods or drinks, while not burning it off as energy expenditure. Strangely enough, sugar is a toxin to the body. When there is excess sugar not used in aerobic metabolic processes, the body converts it to something that can't hurt it – fat. That energy is stored away as fat until the fat stores reach capacity. Then the sugars find their way back into the bloodstream, and the person becomes diabetic (a simplified view). What happens in diabetes? The excess sugar is toxic to retina, neurons, vasculature, and heart muscle – long term, uncontrolled diabetics develop retinopathies (blindness), neuropathies (pain), peripheral arterial disease (have problems with circulation in lower extremities), and cardiovascular disease, which seems to be an effect apart from that coming from atherogenic cholesterol. So the key is to have low sugar consumption and exercise! Fatty liver seems to arise when the body starts to store fat in places other than fat depots – called ectopic fat – and is usually coincident with emerging insulin resistance. As obesity develops, fat gets stored in the liver (and around the heart!). In some people, there are progressive inflammatory changes in the liver that lead to tissue damage and a condition call non-alcoholic steatohepatitis (NASH); its not yet know how or why some people go on to this more advance stage of liver disease. The incidence of fatty liver is also on the rise with the rising tide of obesity, even in teenagers. The sobering thought is that the only treatment is to lose weight – usually the steatosis (fatty liver) dimishes.

Hi Ingrid! Many thanks for doing this AMA! I've asked a similar question in an AMA related to diabetes, but I'll ask it here too.

Obviously there's a worldwide problem with obesity, and associated diseases like diabetes and various heart problems. How much of a factor do you think that education (or lack thereof) about healthy eating, exercise and related areas at an early age plays into this pandemic? Or do you think that people are educated well enough on these topics and, not being able to think of a better way to phrase it, simply 'do not care'?

OldBoltonian

Obesity is an issue of growing concern that is projected to become a leading public health problem because of the associated morbidities such as diabetes, heart disease, hypertension, certain cancers, asthma, gall bladder disease, osteoarthritis, and psychosocial burden – people feel bad. The rates of obesity have steadily grown over the last 50 years, and there has been a lot of thinking about why that might be. Our genes aren't changing appreciably, but our environment has changed a whole lot to one that is obesogenic. Consider: lack of physical activity (people drive everywhere, or even do their business online from their couch), the rise of calorie-dense, nutrient poor convenience foods, the increasing stress of life (many people self-soothe by eating), and even having heating and air-conditioning everywhere! We even no longer have to spend energy to maintain our body temperature, putting our resting metabolic rate at an all time low. Many people still think that obesity is the result when people simply don't have enough will power. To a certain extent that's true, BUT a realization that brain signaling plays a large role in feeding habits is a very important insight. And there is some evidence that the widespread availability of processed foods has contributed to the deregulation of our signaling pathways so that we keep eating foods that taste good, but have no nutritive value, without stopping (remember the ad for potato chips – you can't eat just one? That's what I'm talking about.) These neuroendocrine signals are powerful drivers of behavior and it is really difficult to continually muster the will power to do otherwise – eat fresh, healthy food in moderation, minimize sugar consumption, exercise. These are the messages that are taught by educating people about a healthy lifestyle, yet the proportion of people becoming obese continues to rise, and people who lose weight often put it back on. Education is absolutely important, the earlier, the better. But often, these principles fly in the face of our prevailing culture. I've often wondered how much better off we could be if we did things like: instead of the long line of gas-guzzling SUVs dropping off kids to their schools, we would instead build safe bike lanes so kids could ride in.

Hi Ingrid, what are your thoughts on the ketogenic diet?

Ancalagon1

Good information on dietary recommendations is hard to come by, and there is a lot of confusion among professionals and consumers alike. There are groups conducting trials in both men and mice on the ketogenic diet, which is an exteme form of a low-carbohydrate diet. The preliminary results are good – preferential loss of fat (utilizes fat as an energy source), improved cardiovascular lipid profiles, improved glycemic profile, even decreased appetite, a greater sense of satiety and fullness, and improved athletic performance. Even less extreme forms like South Beach, Atkins, and even paleo appear to bring some of these benefits.

Hi Ingrid, It seems that common belief is that medications are just band aid approaches to when it comes to obesity and heart disease, how do you feel about the idea that money would be better spent in nutrition and physical fitness programs to create long term health benefits as opposed to being reliant on medication?

superman127

I actually really appreciate this question. I'm also a yogi and hold deeply the values of healthy, natural

living and would always advise people to create an environment around them that supports fresh, wholesome food, company, and activities. But just as herbal medicine doesn't cut it when someone is battling cancer, there is a growing number of morbidly obese people who need some help with an effective therapy. The idea would be to build a healthy and fit lifestyle on the foundation of a treatment - maybe with the hope that at some point, the treatment could be dropped.

Is there any evidence that obesity changes DNA in children of obese parents? For example, if mom is very overweight and has type 2 diabetes as a complication from her obesity, if she focuses on teaching her children proper nutrition, coping skills, avoiding processed foods etc, will they still be at a higher risk for those 2 diabetes later in life?

curiouserthangeorge

That's a great question. There is emerging evidence that obesity in parents, especially mothers, can influence the risk of obesity in offspring (and metabolic dysfunction later in life), but not by changing the DNA directly, but by epigenetic changes. By that, I mean that the DNA markings may be changed that influence an altered gene expression pattern that may be more obesogenic. Some of those sorts of epigenetic marks may be acquired (remember Lamarck?) in response to environmental factors and even passed on to offspring. Another fascinating possibility is the role of the gut microbiome in obesity. It is normal to have a population of bacteria living in our guts – they live there symbiotically and even help digest our food and modulate our inflammatory responses. There is evidence to suggest that that the microbiome composition influences the calorie harvest from our foods, so we may be getting more calories from our diet. The microbiome composition of babies is "inoculated" from the mother during birth, so that factor also can appear heritable.

Thank you for doing this AMA. I am currently a PhD student focusing on Environmental Health, with training fellowships in Biostatistics and Toxicology/Pharmacology. I am fascinated by the Gene-Environment-Development interactions of complex diseases. What advice would you give to young investigators, and what additional skills would you recommend students learn to be successful in your field?

I recently listened to the Genes Channel on audible where it was mentioned that nanoparticles are being used to repair "bad" genes, is this an area of research that will gain more traction? It seems that it would prove a great opportunity for pharmacogenetics and nanotechnology to merge together.

Thank you for your work!

purpleyoshi911

I excited that you are interested in this field, and that of gene-environment interactions. I think this is a field whose time is coming, especially with the Precision Medicine Initiative (PMI). This audacious project will spur the development of devices to measure people's exposures to environmental factors with a level of precision never before achieved. I see a lot of activity for such large collections of data (as one needs large data to have sufficient power to identify interactions in observational studies). Even as we continue to move toward big data and bioinformatics, I think there is still an important role for clear biostatistical thinking to make sure we're working in an inferential framework.

You say :

obesity is a disease of the brain! It has a lot to do with messaging

We know saturated fats have the benefit of satiating our appetites. We also recently discovered from this article that the **hypothesis** that saturated fats cause heart disease was incorrect.

How much research have you done into the role of saturated fats in our diets?

gerbil-ear

None myself. I would refer to the literature.

I'm currently a Biostatistics PhD student and I'd like to ask about the statistical part of your job.

What methods do you find yourself using most often when analyzing data? What are some of the biggest weaknesses you have found with the current methods? Do you expect an increased need for statisticians in genomic medicine?

rem14

Analytical methods! One of my favorite topics! For testing genotype-phenotypes associations, we commonly use linear models including regression, logistic regression, Cox models (time-to-event), often in a mixed-model framework (to account for family relationships in our data). Multivariate models and meta-analysis techniques (not for just combining results across studies, but actually doing secondary analysis of genomwide association results datasets) are also frequently used. Bayesian networks, machine learning computational techniques, and a partridge in a pear tree … ☺ One of the most challenging aspects of statistical analysis is that programs for doing even simple analysis often break in "Big Data" applications. We're re-working our pipeline now to ensure we can handle at least 100,000 subjects in a single analysis – it also has implications for the computational footprint. Bioinformatics skills are also required in my group, both for handling big data as well as integrating information from publicly available knowledge databases. Yes, I see a continuing (big) need for biostatisticians in the genomic age – I'm trying to hire one now!

Hi Professor Borecki,

Thank you for doing this AMA! I am curious about your Genome-wide association studies.

Many GWAS studies have failed to identify clinically relevant variants. Do you think that in future re-analyzing the existing datasets using new (yet to be developed) methods may enable some of the statistical problems and biological (variation) issues associated with GWAS to be overcome?

Thanks

ClaireAtMeta

I'd like to start this answer by saying the glass is half-full! Some studies have succeeded in identifying some clinically relevant variants. Of course, we're interested in further progress! One of the feature of GWAS studies is that it queries common variants / haplotypes, that predominantly are found in the ~94% of the genome that is non-coding region – many of the clinically-actionable findings from GWAS are common exonic variants with some putative effect on protein structure / function. Recent insights from projects like ENCODE suggest that the bulk of GWAS hits sit in regions that may have regulatory function (eg promoters, enhancers, non-coding RNAs). To me, this speaks to homeostatic mechanisms that may be more responsible for fine-tuning the coordinated gene expression profiles within individuals. Re-analysis of GWAS data might reveal additional clinically-relevant variants when imputing lower frequency variants (especially in exons). But a more direct approach might be sequencing and analysis of the exome, which contains a vast reservoir of rarer variation in conserved sequence with a higher prior expectation that a variant may have effects on clinically-relevant

phenotypes. I'm interested in a genomic view that integrated putative regulatory sequence (via expression QTLs) and exonic sequence to refine our models of the genomic architecture of complex diseases.

Sounds like great work, and thank you for it!

Out of curiosity, where do you obtain the genetic information to do this work?

With recent articles about the government requesting DNA from organisations like ancestry and 23andme, have you ever had any experience or heard of the government requesting genetic information from researchers?

KatCole7

Thanks for this question – you need good data to fuel your discovery efforts! We are Regeneron are building a portfolio of studies with collaborators in a variety of areas. Our flagship collaboration is with the Geisinger Health System of NE Pennsylvania. We have consented over 100,000 subjects thus far on our way to the goal of 250,000 subjects, in which we will use electronic health records along with sequence data to find disease-associated variants. We are also collaborating with investigators who have epidemiological studies (of a few thousand subjects) with deep phenotype data in areas of strategic interest, as well as samples from a variety of founder populations in which bottleneck and drift have restricted the allelic spectrum and allowed some deleterious alleles to drift to higher frequencies. We provide exome sequencing for our collaborators for the opportunity to analyze and mine the data. As for the government, they are in the business of providing funding for research programs to move genomics and personalized medicine along (https://www.nih.gov/precision-medicine-initiative-cohort-program). Its an exciting time to be in the field of genomic medicine!

Where do you see statistical genetics going after GWAS? Do you see think that Common Disease-Rare Variant (CD-RV) will be investigated less because of the lower extent of applicability? How do you think drugs will be developed for traits that are extremely complex and involving many pathways/tissues/organs?

OnQuh

Very insightful question, thanks. There are different goals – discovery of variants that are actionable and then simply understanding the underlying biology. I think common variants are a vital piece of the puzzle, and my research interests were in relating common (likely regulatory) variants to their targets and networks. Its important to know that up or down regulating a gene or set of genes has an effect on risk of disease. I even see this fundamental work to understand the biological basis of complex traits (including other omics) as the more important goal. I can imagine situations in which a deeper understanding of the biology of a complex disease may nominate therapeutic targets not readily identified by simple association studies. If pathways can be identified, it may be that other genes may be more approachable as targets than those that brought attention to the pathway. Many medicines have a specific target, despite a complex etiologic architecture, therefore, the potential of a target can't be judged by its marginal effect alone. If tissue-specificity is needed, the possibility of CRISPR modification of relevant tissues arises. We are at a remarkable point in time where out technological tools offer a variety of creative possibilities for drug development.

Hello,

Thank you for taking the time to do this AMA.

I am interested in your thoughts about how some researchers have characterized Alzheimer's Disease as a sort of "diabetes of the brain" or "Type III diabetes". I believe these researchers argue that Alzheimer's Disease is the result of a complex interaction between insulin-resistance and neural inflammation that leads to progressive apoptosis, via neurofibrilliary tangles that cinch the microtubules (at least in part). Based on your knowledge and experience in your area, (and I am hoping that you have read about this research), do you think there is credence to the idea that Alzheimer's Disease is partly the result of progressive neuron-level diabetes and inflammation? Why or why not?

My second question is about the new medicines you have identified. Which medicines have you identified and how do they differ from previous medicines? Why do you predict that these new medicines will offer any advantage over the old medicines? Is there a new class of medications for treatment of obesity (or metabolic syndrome or cardiovascular disease) that treat the causes rather than the effects of cardiovascular disease? If so, how do they (or how are they predicted to) decrease the likelihood of cardiovascular disease?

My third question is about the under-powered genetic studies you meta-analyzed. If these studies were under-powered even with 1000s of subjects per study, do you think that the meta-analyses and other related studies conducted might be chasing a null effect? That is, maybe there are other causal factors that contribute more (independently or interactively) to cardiovascular disease (and similarly related outcomes) than the ones used in the under-powered studies. Also, even if the detected effects are actually there, their effect sizes may be so small that one should consider looking for causal factors that would generate larger effect sizes. So, which causal factors generate the largest effect sizes in better understanding cardiovascular disease and its related outcome measures?

dbzgtfan4ever

Great questions, thanks. The idea of finding a new perspective on Alzheimer's disease is very attractive. There are epidemiological data suggesting that diabetics have an increased risk of Alzheimer's dementia. Then there's a recent report that progression may be affected by immune cells gone awry in pruning brain neuronal connections (http://www.sciencemag.org/news/2016/03/over-pruning-synapses-may-drive-early-stage-alzheimer-s-disease?utm_source=sciencemagazine&utm_medium=facebook-text&utm_campaign=alzhapses-3369). These observations both support this notion, but more research is needed to nail this down. I'm excited by this line of investigation.

We hypothesize that medicines developed on the basis of genomic findings are more likely to be effective, are more likely to address causal factors (rather than symptoms), and side effects can be anticipated by looking for effects of the gene on other measures of health. This is new and only become possible recently. They are also likely to have great specificity, and could be used in individuals with genomic indications (personalized medicines). Yes, such observation can frame new drug development (see http://www.nejm.org/doi/full/10.1056/NEJMoa1510926).

Your third query was about individually underpowered studies and meta-analysis. The idea is that combining several / many underpowered studies by meta-analysis increases the power for discovery – as if all the data were analyzed together. Many meta-analysis efforts have put together 10's or 100's of thousands of observations, which has made it possible to detect the effects of variants whose marginal effectsizes are modest – but whose discovery has provided profound insights into the underlying mechanisms and etiology of complex traits.

Okay... I get that I need to eat sensible portions (preferably of healthy food) to lose weight.

But that sucks and makes life way less enjoyable.

I've also heard of recent studies in mice that have successfully allowed them to eat more calories than

they should while still maintaining a svelte mousey physique.

How long is it going to be before overweight people like myself can just pop a pill before meals (or whenever) and have a reasonable expectation of attaining a body that isn't embarrassing in a swimsuit?

As a 40-year old, is there any hope of it happening in my lifetime (before being a bit overweight kills me), or am I going to be stuck in this Sisyphean cycle of exercising and eating salad for dinner for the rest of my God forsaken days?

jollyswagman

I don't think the principles of healthy living can ever be set aside by taking a pill and then eating and doing whatever we want, but some kind of therapy is sorely needed. This is an area that I am personally working to advance since joining Regeneron last year.

Hi Ingrid, thank you for allowing us to ask you questions! Although a basic question I'm curious. Ive been taught that is sugar is responsible for a huge number of diseases such as Diabetes etc. I myself tend to drink maybe one or two energy drinks while at work sometimes 5 days a week. In terms of my health is this dangerous for me in later life? I've always heard about the "dangers" but this has been through articles on the Daily(Fail)mail which I struggle to believe 100%. Thanks again!

rammen4

Like anything, a little sugar in moderation is fine, especially if you're physically active and burning it off. That's presuming you're otherwise eating a healthy diet.

Thanks for doing the AMA. Is it true by 2030 that almost 70-75% of Americans will officially be obese and have big time health issues ? I'm a physical trainer and I read an article about this.

iownablender

Such extrapolations of current trends depend on assumptions - like the current rate of increase in the prevalence of obesity will continue in a linear fashion. I don't know if I'd bet on this estimate (70-75%), but no doubt, the numbers continue to rise. There are interesting observations from populations in Samoa, where the rate of obesity was ~55% in 2008. The BMIs (in $kg/m^{2)}$ were well into the 40s and 50s (really high), and were showing no compression that might indicate some biological limit to how high they could go. That is a sobering thought. No doubt that obesity brings bit time health issues. I don't know how dire the situation may become, but its possible that it will continue to affect more people, more profoundly.

Hello Ingrid, your team's research sounds like a search for the holy grail of medicine! Have you identified any specific drug targets yet?

chefymum

Yes! Our job here is to use insights from genomic analysis to nominate targets that may be good drug targets. The most recent success story is regarding Praluent (a PCSK9 inhibitor). The story begins when two variants in PCSK9 were identified associated with familial hypercholesterolemia. A subsequent study identified a loss-of-function variant in PCSK9 that was associated with low cholesterol levels and reduced risk of coronary heart disease, suggesting that if one could take down PCSK9 levels, it may have a therapeutic effect. Regeneron developed a monoclonal antibody and

through many studies and trials, showed that it reduced both cholesterol levels and risk of CHD (Stein et al, 2012; http://www.nejm.org/doi/full/10.1056/NEJMoa1105803). We received FDA approval last August.

What advice would you have for an undergrad majoring in genetics that wishes to go into academia? What was the biggest obstacle you faced in your career?

ZebraSweet

Get into a lab and start doing research as soon as possible. Good graduate programs look for undergrads who already have research experience. I recommend post-doctoral training. Faculty positions are competitive and having those post-doc training years to build up publications and start writing grants is a big help. Perseverance is probably the most important ingredient for success. Good luck!

Why is this a question geneticists are still pursuing instead of social psychologists?

maniclurker

Because in the absence of meaningful treatments apart from bariatric surgery, its important to follow all leads. There are people who are pursuing the behavioral therapy route (eg, https://psychweb.wustl.edu/wilfley), and many extant programs leverage soc psych concepts such as journaling, social support, accountability, developing healthy habits, etc., like Weight Watchers, Take Off Pounds Sensibly (TOPS), and so on.

Agree or disagree: The drug of tomorrow is proper nutrition.

doomcomplex

Let food be thy medicine and medicine be thy food (attributed to Hippocrates). Agree for support of wellness (neglected in our current medical delivery system). Disagree for serious illnesses, although proper nutrition can be a powerful supportive therapy.