[MUSIC PLAYING]

JUAN CARLOS CELEDON: Thank you for the kind introduction, and it's a pleasure to be here. As a matter of disclosure, I have received research materials from Merck, GSK, and Pharmabide, all just to provide medications free, of course, to children participating in NIH funded studies. The learning objectives for this session are first, to understand, establish the potential risk factors for asthma and health disparities for asthma in childhood, discuss existing evidence to support the role of vitamin D, psychosocial stress, and overweight or obesity in asthma pathogenesis, to comprehend how genetic and epigenetic studies will help us develop personalized medicine for asthma, and to understand the impact of adequate use of control or medications on reducing asthma disparities.

So as you all know, asthma is the most common chronic respiratory disease of childhood. It poses enormous cost to society and to the health care system, estimated as over $80 billion per year. But asthma is not an equal opportunity disease. So when you look at this data, childhood asthma is more common among the poor. It's more common if you compare blacks to whites and more common in blacks. Now, if you look at Hispanics as a group, it looks as if they had less asthma than blacks and even whites. But that's a fallacy. And the reason for the fallacy is that Hispanic or Latino is a term coined by the US Census.

If you go to Latin America, nobody will know what a Hispanic is. This was developed by the US Census. So by definition, it refers to people whose origin can be traced to lands that were previously under Spanish control. So anybody who can trace its origin to large parts of the US, Mexico, Central and South America, some Caribbean Islands, and Spain are considered Hispanic by the US Census. Hispanic is therefore, ethnicity and not a race.

This is a huge misconception. Here, you have five people who would check Hispanic when they answered a census survey. Rigoberta Menchú, who's a Mayan Indian from Guatemala, to players from my favorite team the Red Sox, Mike Lowell, who's Puerto Rican of Cuban descent and has predominantly European ancestry, and David Papi Ortiz, who's Dominican of African descent. You have Shakira, who is from my hometown, from Barranquilla, Colombia. Her father is Lebanese. She would be Hispanic. And you have Alberto Fujimori, who's Peruvian but whose parents are Japanese. He would also check Hispanic.

So studying Hispanics as a group, it's most of the times, not always, not helpful in biomedical research. In fact, when you separate the Hispanic subgroups in more detail, it turns out that Puerto Ricans have the greatest burden from childhood asthma, no matter how you assess that. Whereas, disease frequency, morbidity, or mortality from asthma of all ethnic groups in the US. Whereas, Mexicans have the lowest burden from asthma. This is the so-called Hispanic paradox.

You see this not only for asthma but for premature birth. When you look at the US states and its territories, Puerto Ricans deliver the most preemies and Mexican women deliver the fewest. So why is that? It's obviously multifactorial. And there are factors at the individual level and factors at the community level. The only one that is not modifiable yet is genetics.

Everything else is potentially modifiable, including socioeconomic status, indoor pollutants, environmental tobacco smoke, perhaps vitamin D status, stress on violence, access to health care, literacy, and cultural health belief. In the community level, you have some of the same players and then you add things like housing conditions, stress on violence in our communities, outdoor pollution, education, and the wheel goes on and on.

So let me start by talking about racial ancestry. So this is a paper we did a few years back with John Brehm. And what we did is, here you have a plot of the racial ancestry of 700 approximately Puerto Rican children. Puerto Ricans are on average, 25% African, 10% to 12% Native American, and the rest is European. So Puerto Rican kids are the red dots. Here, it's European ancestry, here is African ancestry, and here is Native American ancestry. That's the average. Some of these kids are predominantly African. Some of these kids are purely European. And some have more Native American ancestry. So there is interindividual variability in ancestry.

And what we found assessing this with genetic markers is that the proportion, the global proportion of African ancestry in these children is inversely related to their lung function. So the pre and post bronchodilator, FEV1 and FVC, are lower as the proportion of African ancestry increases. This is after accounting for access to care, insurance, use of medication, a many other potential confounders.

This has been replicated in African-American adults in a large study, where, in African-Americans, there is also variability in the proportion of African ancestry. And in African-Americans the proportion of African ancestry was inversely related to lung function. This is Costa Rica and I've told this story before, four years ago in Grand Rounds. When I was a research fellow at Harvard, I was attending my first meeting. And there was a professor who said, I've heard you want to do research in Costa Rica. You have to talk to me because I practically own the island. I said, bless your heart.

So Costa Rica is a Central American country situated between Nicaragua and Panama. Most Costa Ricans descend from 4,000 people who inhabited the Central Valley. And there were about [INAUDIBLE] Spaniards and 1,400 Native Americans. There were very few African slaves in that era. That was a census in the 1600s. From those people, they sent approximately four million contemporary Costa Ricans. So you can go back and trace their ancestry, their lineage to the Central Valley, you have what's called, a founder population.

These are now adolescents and adults. This is work done with Wei Chen, in my group, and John Brehm. And you have the same exercise, but now, these adolescents and adults are the green dots. And Costa Ricans are predominantly European and Native American. They have very little African ancestry. They are about 60% to 65% European, 30% to 35% Native American. And it turns out that in this population, you see the opposite phenomenon when you study Native American ancestry. So Native American ancestry is associated with higher FEV1, higher FVC, and higher FEV1/FVC ratio.

This has been replicated also, extensively in both children and adults. This is a meta-analysis of thousands of racially mixed Hispanics, study published in 2015. And this is asthma now, not lung function. What this study found was that in these racially mixed Hispanics, Native American ancestry was inversely associated with us, or at least, appeared to be protective. And African ancestry appeared to be detrimental.

So we think, and others do-- that this partially explains in a very coarse, shallow level, this Hispanic paradox. The temptation here, if you are a racist, is to say that a particular-- that African ancestry, for instance, is associated with mutations that make these people inferior somehow. But that's an overly simplistic explanation because ancestry is also a marker of environment, and lifestyle, and culture. And that is very important to remember.

So now I'm going to move to genetics and epigenetics. So when I wrote my first grant to the NIH, my first R01 grant, a few years back, I wanted to do a study in Costa Rica. And I got one of the reviews, reviewer 3, the infamous reviewer 3 said, you know, you should only study this in whites. These Hispanics are too complicated. So this is 2003, you know. This is a study with Matt [INAUDIBLE] who's currently an associate professor at Harvard, one of my trainees, looking at a gene called, matrix metalloproteinase 12, which had been associated with emphysema in mouse models by Dr. Steve Shapiro, who's our chief medical officer now, here at UPMC, and by Jack Elias, who's the dean of Brown now. He has shown that MMPs were associated with higher interleukin-13 in transgenic models and asthma. So I said, this is an interesting gene to take a look at.

So what we did was we first looked at this in Costa Rican children, a large study of Costa Rican children. And found that there was a variant, a SNAP, in the promoter of this gene that was associated with higher lung function. And the lung function of people who had this SNAP was higher. So we did the opposite of what the reviewer said. We went from a racially mixed population to European and African populations, and in fact, replicated the finding.

We then went on to look at this variant in a large study of adults now. These were study of veterans of war. They were enrolled when they were 40 years old. They had 20 to 30 years of follow up with multiple pulmonary function test, and found that the SNAP that predicted higher lung function in children with asthma was associated with lower rates of COPD over three years of follow up. Time-- this hypothesis that some children with asthma will go on to develop COPD. But the reason I'm showing you this is to illustrate that it's a fallacy that studying a minority population cannot yield to benefits to the greater population, that studying minority population is good for all of us.

So this is a study from 2011, where many of us put together a multi-ethnic cohorts to study asthma genetics. There were thousands of patients of non-Hispanic whites, Hispanics of several subgroups, and African-Americans. And this is the most highly replicated finding in asthma. I don't think anybody in 2018 would dispute the fact that in these locus on the long arm of chromosome 17-- that locus confers a higher risk of asthma. How this works is still being studied. It's a very complicated genetic locus containing several genes. It appears that this one or MDL3 may be the most important. And it has to do with airway epithelial integrity, I'll come back to that. But there were others.

So last year, we were finally able to put together several cohorts of Puerto Rican-- three cohorts of Puerto Rican children, a very high risk population, together with a cohort of Puerto Rican adults. It's about 5,000 people-- to look at a GWAS, a combined GWAS of asthma. And what we found is that that locus-- that appears to be highly replicable-- about all racial or ethnic groups is most important in Puerto Ricans-- the 17q21 locus, very highly significant. We were also able to replicate strong findings for genetic variants in other genes, including one of the receptors for interleukin-1 and thymic stromal lymphopoietin, but not for interleukin-33.

So at that time-- this was published last year-- we said the next step is to conduct GWIS, which is Genome Wide Interaction Studies, looking at environmental exposures and also studies of the epigenome. So why are we interested in epigenome and why are we interested in environment? This is a sobering finding. So Francois [INAUDIBLE] put together data from over 120,000 control subjects and over 50,000 subjects with asthma worldwide. This was the largest GWAS of asthma ever done. And they identified 19 genetic loci or data associated with asthma. But when you put all of that together, only 5%, less than 5% of the variability of asthma is explained.

So why is that? It's common sense. So if you look at this data, it's a data for childhood asthma. And in some of these countries there was data in the 1960s-- data from the 1960s and data from the 1980s, 1990s. There has been a huge increase in prevalence of asthma in some of these countries. Now, some of you may say, well, that's diagnostic bias. Asthma is better diagnosed these days. I don't think that explains this. But whatever happened with this epidemic that we're observing for asthma and allergies, it cannot be genetics alone. The rate of mutation in humans is extremely low. Something changed in our environment and lifestyle over the last century. That interacting with genetic variants that confers shiftability caused the disease.

So in that context, we're very interested in looking at epigenetics. What is epigenetics? It's the programming of gene expression that does not depend on your DNA code. It has some characteristics. It's modifiable, potentially. It can be reprogrammed. It's active or it's poised to be activated. But this is very important and I will come back to this. This is tissue or cell specific.

So if I took samples from all of you in the audience, anybody, and I took samples from your hair, I took samples from your mouth, saliva, I took samples from your white blood cells, and ran your DNA sequencing in the same machine and there was no technical error, I should get almost the same DNA sequence. However, if I do the same exercise and now I look at DNA methylation in your different dishes, it's going to be unique to every tissue in your body. The epigenome is cell or tissue specific. So if there is one thing you can remember, remember that.

So one of the ways this works is through methylation of DNA. Methyl marks are added to certain DNA basis. And that not always but often represses transcription of the gene. The opposite is true. There is hypomethylation, the gene often is more transcribed. So the first study I'll show is an epigenome wide association study of total immunoglobulin E, or total IgE in Hispanic or Latino children. This is a very important intermediate phenotype, and it's a therapeutic target. So some of you will use anti-IgE or a pair of anti-IgE for severe asthma.

And there have been a study in populations of European descent that was published in *Nature.* And if you look at that, they found thousands of markets associated with total IgE. And I've been doing genetics for quite some time, and I was a little bit curious as to why they had so many positive results. But one thing they didn't do is-- this was DNA from white blood cells, and all of you know when you get your CBC and differential, the white blood cell count represent different types of cells. They're neutrophils. They are lymphocytes. They're monocytes. It's different. They're eosinophils.

So we repeated this exercise taking data from Mexican and Puerto Rican children. But we did this study adjusting for the differential cell count, that is, for a time. And this is what we found. So this is what's called, a Manhattan plot, bear with me. These are the chromosomes. And this is P value. Anything above this black line is supposedly significant. That looks like a Christmas tree. There is a ton of positive signals.

And there is tremendous deviation. That red line-- so you'd expect under the null hypothesis, this is a tremendous deviation. The second analysis is when you adjust for the type of cells. And then you only get four positive signals. But the signals that you get when you do that are very biologically plausible. They're important. So one of these genes is seeing [INAUDIBLE] type 1. It suppress expression of IL-4, which is importing allergy. It induces expression of interferon gamma in T cells and reduces allergic immune responses. And the origin, ACOT7-- there is a lot of experimental data to implicate any asthma.

But one thing that I mentioned, I said to you I would come to before, is the realization over the last five years, I would say, that the money-- if we are to find what is causing this epidemic, it's in the airway epithelium. There is increasing evidence that that is probably the case. And this is just a cartoon from this review, last summer, on the airway epithelium in asthma. And under this conceptual framework, what would happen is, you have a child who has probably some hereditary predisposition. There are some injuries that we have to identify, some environmental injuries with viral pathogens, pollution, pollution in the home, allergens. Their airway epithelial barrier is disrupted. That allows these injurious agents to penetrate under the epithelium, interact with dendritic cells, and it starts a cascade of events that leads to allergy and asthma.

In fact, when you look at these 19 genes that have been identified by these mega GWAS, what sticks out is that some of these genes are very relevant to airway epithelial barrier integrity. So our MDL3, for instance, if it's overexpressed, in mice, it decreases [INAUDIBLE] lipid levels, increases inflammation, and we're remodeling. And if this is expressed in pulmonary epithelium, you can induce experimental asthma, [INAUDIBLE] induced asthma. And there are all these genes that have been linked to epithelial activation damage and type 2 immunity. Two really interesting genes to us, CDHR3 and PCDH1, are very important in cell adhesion.

So five years ago, we thought of this when writing a grant for our study in Puerto Rico. And it's cartoon that Dr. Supinda Bunyavanich, who worked with me when I was in Boston, showed in a prior presentation. She's just published this. What she's doing is transcription. We're doing both methylation and transcription, but the cartoon serves the purpose, just to show you, what we do. We take samples. A child will have asthma, we'll have controls. We do phenotyping. And we take samples from their nose. We do a nasal brushes and nasal curating and obtain both DNA and RNA for studies of methylation and expression.

We do, not only RNA sequencing, as is shown here, but genome wide study, so methylation. We run the data in the lab. We do some analysis. And we compare cases and controls. There's a very easy way to explain this. So the question that you could all ask me is why are you a studying nasal epithelium? And you know that in kids, doing bronchoscopy, seeing 1,000 children-- it's not going to fly by any IRB that I know.

But both methylation and expression in nasal epithelium in nonsmokers, and most children do not smoke, are very strongly correlated. The correlation is not 100%, but it's very good. So in this case, the nose is a window into the lung. And this is what we've found. So you have the Christmas tree, but these are single cells. These are nasal epithelial cells now. There are many signals that are associated, and there is that deviation. But what was really interesting to us is-- most of these methylation marks that were associated with ectopic asthma also affect gene transcription, which is very reassuring. These things are affecting gene function and therefore, are more likely to be relevant.

But more exciting to us-- what we did in this first study is, we tried to use a panel of these methylation marks. These are CpG, are called, to differentiate children with atopic asthma from control subjects. And using different methods, the predictive value or declassifying value, [INAUDIBLE] study of this is very high. When you look at the literature for asthma using clinical predictors or genes, it's usually in the realm of 60%. With this, we get well over for the area under the curve and accuracy over 90%. But more exciting than this, in what do we do? The name of the game is replication.

So what we did-- we took these panels and we ran them in another cohort of African-American children from my colleague, Ivana Yang in Colorado and a cohort of Dutch children from Dr. Gerard Koppelman in the Netherlands. And we replicated 28 of the top three signals, very highly significant. So the most interesting thing to us is, I was telling you about the airway epithelium-- we found this signal starting airway epithelium in old white blood cells. But also, some of these genes directly are known for a fact, epithelial barrier integrity on function. So it's very interesting. I'll come back to that.

So briefly, I'll tell you about vitamin D. And this is a child in Costa Rica. And I took this picture years ago, when I was doing studies there. And he's desperately trying to get his vitamin D levels up. So this is kind of noontime in San Jose. He's wearing T-shirt, he's wearing shorts. 15 minutes of sun exposure, summertime, will replenish your vitamin D levels. He's also taking milk fortified with vitamin D, so that's all good.

However, it turns out that in Costa Rica, in a study with 28% of children in that country, [INAUDIBLE] near the equator have low levels on their [INAUDIBLE]. So this has been also shown in multiple tropical areas around the world. The sun will not do the kids any good if they don't go out. And with the advantage of technology and video games, they are inside, as you have seen it-- you have kids, all the time.

So in the first study in Costa Rica, we found a link with severe asthma exacerbations in kids of school age. We know that vitamin D has antioxidant effects. We thought that perhaps, that may have something to do also with the detrimental effects of air pollution. So we did a study with Franziska Rosser, one of our faculty, looking at how close children in Puerto Rico live to a major road, which is an indirect marker of pollution. Their vitamin D levels-- severe asthma attacks.

And this is what she found. So in category 1 are kids who live farthest from the highway. And they have normal vitamin D levels. Here you have kids who either have low levels or live close to a highway, but not both. And here, you have the kids who live close to a highway and have low levels. And they have nearly five times increased [INAUDIBLE] of severe asthma attacks.

Another study we did with Sylvia [INAUDIBLE] last year, is looking at these kids with low levels and looking at asthma attacks, but now differentiated allergic asthma from nonallergic asthma. And what we found is, yes, it appeared to be associated with both, atopic and non-atopic. But it appeared to be more strongly associated with non-atopic asthma, which I would relate more to things like viral related illness. So that was very interesting.

So on the basis of all of this, we hypothesized that vitamin D may protect against severe asthma attacks through one of two mechanisms. I didn't show you that data-- either increasing response to steroids or immunomodulating the severity of viral illness. So we're nearly halfway through a multicenter trial, NIH funded, of vitamin D supplementation to previous severe asthma exacerbations in children with asthma, which is called, vitamin D kids asthma. And I really have appreciated the support and again, an old shout for referrals. We're almost there.

So in next area that I will call, very psychosocial is stress exposure to violence and asthma. So this is Dr. Wei Chen, who led this study that I'll briefly tell you about. So Puerto Ricans are often exposed to high levels of violence and stress. It turns out when you look at veterans of the Vietnam War, the group that reported the most PTSD symptoms are Puerto Ricans. Following the events of September 11 of 2001, in New York City, the ethnic group the reported most PTSD symptoms were Puerto Ricans. So they appear to be particularly susceptible to the effects of violence.

In a series of studies, we have shown that childhood abuse, physical or sexual, is associated with greater rates of asthma and greater risk of asthma severity. This was replicated in a longitudinal study of African-American women. Those women who had been abused as girls had a higher risk of developing asthma later in life. The mechanisms for this link, which has been shown not only by our group but by many others are unclear.

So in writing one of these grants, I ran into work by my colleague and now collaborator, Kerry Ressler-- he used to be at Emory's, he's now at Harvard-- who's a psychiatrist. And Kerry had done research on this gene. It's the gene for the receptor of adenylate cyclase-activating polypeptide 1 receptor. I'm going to run out of breath, so I'm going to call it, ADCY. It's just too long. So he implicated this in the pathogenesis of post-traumatic stress disorder in heavily traumatized women. And then he did a follow-up study in children and implicated SNP in this gene in childhood anxiety.

This took him five years. When you read the paper, it's a paper in*Nature.* It covers everything from serum levels of the biomarkers, to genetics, to epigenetics, to mouse models, to brain biopsies. It's a really elegant study. But to my knowledge, he was the first person to ever show in a medical literature, that symptoms of a psychiatric disease, in this case PTSD in this group of women, were associated with methylation of the promoter of the gene. Now, one has to take this data with a grain of salt because this is cross-sectional data. So was it the PTSD that led to methylation, or the opposite? You need the longitudinal data for that but nonetheless, is very interesting.

So what we did-- the first of the series of his studies, was to look at these gene and asthma in our cohort of Puerto Rican kids. And due to time constraints, I will just tell you that both gene that share the same SNP, that he has shown to be associated with PTSD in adults, was shown to be associated with asthma in these kids. We also showed methylation of the promoter of the gene. It's associated with asthma in these Puerto Rican kids. And to my knowledge, that was the first study to provide a potential genetic, epigenetic basis for these stress asthma link. And we said then, and we still believe this. The longitudinal studies are needed.

So this is a child who is using his inhaler very poorly. He's now using a spacer. So I show you this as something you should not do, not something you should do. But another thing about Puerto Ricans, at this point, you're saying, these Puerto Ricans are very unfortunate. And to some degree is true. They have several problems in regards to asthma. One of them is, it had been consistently shown in kids and adults, to have a poorer response to albuterol than members of other ethnic groups. So my colleague, Esteban Burchard at UCSF attributed this finding to genetic mutations in the receptor for albuterol, ADRB2, 4-beta to adrenergic drugs.

However, I ran into this paper by Greg Miller, who's a psychologist at Northwestern and also a collaborator. And what Greg did was very simple. He took white blood cells of kids with asthma. And he had four groups. One of these groups had no chronic or acute stress. I'd like to meet those kids. Another group had acute stress but not chronic. And another group had chronic but not acute. And another one had chronic and acute stress.

So that was it. And he started gene expression in white blood cells of these four groups of kids. And he found out that in the highly stressed kids, expression of ADRB2, the receptor for the [INAUDIBLE] beta-2 agonist, and the glucocorticosteroids receptor was decreased eight to tenfold, times. So I said, that's kind of interesting.

So a question that we posed was-- could stress partly explain why Puerto Ricans respond poorly to albuterol. And this is what we found. So on top of this, you have our Puerto Rican kids with asthma who had bronchodilator response measure. And they had-- this is percent, 3.9% in children this age 8%, is what we can see are positive for research of study. So this would be almost 50% of what we consider a positive response.

We went to a second cohort. This is in Rhode Island and Puerto Rico. So these kids were white, Dominican, and Puerto Rican. And they had data on anxiety panic and anxiety panic disorder. And in children and adolescents with anxiety and panic disorder, we found a reduction response to albuterol. So the question that you would all ask at this point is, well, you're seeing this because the children that are stressed, their mothers are stressed, and therefore, they are not giving these kids a control of their medications. You see, it's all nonadherence.

We went to a cohort of children in a nationwide study called [INAUDIBLE]. And we found a subgroup of kids who had a spirometry evidence of airflow obstructions. They had a low FEV1/FVC. But they had never been diagnosed with asthma, and they were not taking asthma medications. And in those children, interestingly enough, high levels of anxiety or stress were associated with a reduction in [INAUDIBLE].

So we went back to the gene that I've been telling you about. And we put together seven cohorts of children. So here are non-Hispanic whites, Puerto Ricans, Mexicans, and African-Americans, in total 2,700 kids. And found that there is a genetic variant that is associated with a modest but significant reduced response to brochodilators. And then Kerry Ressler, this friend of mine, the psychiatrist, said, you know, I have a group of African-American women living in inner city Atlanta, in whom we have genetic data and we have functional MRIs of the brain.

And what you are seeing here is evidence that the SNP, or the variant, the allele, that was associated with a reduced response to bronchodilators was also associated with increased connectivity of the amygdala and the insula in these women, which is a radiologic marker of anxiety in humans. So how do you put all of this long story together? I didn't show you this, but the genetic variant was also associated with what we call, trans or a distant effect with reduced expression of ADRB2.

So we're saying that this a combination of heredity and environment. That children who have this hereditary predisposition and high levels of distress, have a persistent secretion of catecholamines, and the receptor is down-regulated over time. And therefore, they don't respond to it as well. So obviously, you can extrapolate that or do a study of all diseases in which beta receptors are important. So now, for two minutes I'll talk about PTSD.

So I told you that PTSD has been linked to asthma. We did a longitudinal study. So for two slides, you'll indulge me. I'm going to talk about adults. So this is a study of the World Trade Center cohort. Everybody who helped rescue and recovery workers, 9/11, I enrolled these cohort except firemen, OK? And they had data on PTSD symptoms, a baseline. And then they had been followed for 4 and 1/2 years with PFTs questionnaires, et cetera. So we identified a group of 37,057 adults who had never been diagnosed with asthma before 9/11, and who had never smoked. And this is what we found is the gist of the paper.

Those who had PTSD, pro PTSD at baseline had 2.4 times increase of incident or new onset asthma during the 4 and 1/2 years follow-up. So when you put everything together, there is a very large body of evidence now that suggests that there is something about psychosocial distress. For sure, that makes asthma worse. I didn't show your prenatal studies, but there is also a very large prenatal literature suggesting that prenatal stress may also be implicated in this. So [INAUDIBLE] yet but we're moving towards that to asthma inception. The data is moving in that direction.

So obesity-- so it's Dr. Erick Forno, who's also a faculty member in our group, who's led all these studies on obesity and asthma. And this was the first of several studies that Erick has done. And this was the first demonstration in the literature that children who are overweight or obese have reduced response to inhaled steroids.

In fact, Dr. Dale Umetsu, who's an allergist at Harvard, at Boston Children's, when I was there, and who has moved to Genentech after this paper did this study. So this is a mouse model of obese, experimental asthma. And what he found in this study published in *Nature Medicine,* is that in these mice-- this obese asthma is not mediated by Th2 or allergic immune responses, but it appears to be mediated by neutrophils, Th17 driven responses, and the Inflammation, which is kind of consistent with the fact that these children do not respond to inhaled steroids. Children who respond to inhaled steroids tend to have more allergic immune responses.

So to test this in humans, with Dr. Yueh Han and Erick Forno, we'll look at nationwide data in children and adolescents in [INAUDIBLE]. And what we see here is BMI, body mass index, in these children in quartiles and their risk of asthma. On the left hand side, you have kids who had low levels of fractional exhaled nitric oxide. That suggests that they have non-eosinophilic, nonallergic airway inflammation. And in those children, as their BMI goes up, so does the rates of asthma.

On the right side, you had kids who had high levels of phenome. And in those kids, there's almost a flatline, which is consistent with the mouse model. More recently, aerial look at obesity and this complicated were airway dysanapsis. So dysanapsis refers to this phenomenon, where there is an incongruence and long growth, whereby long volumes grow faster than airway caliber. So typically, patients have a low FEV1/FVC ratio, but they have a normal FEV1/FVC. And what we did with Dr. Daniel Weiner was to collect data on BMI, obesity, and dysanapsis in six cohorts of children across the US and Europe. 4,156 kids were included this study. We did some study snapshot, cross-sectional and some longitudinal. And then in kids with asthma, we looked at clinical outcomes.

And this is what we've found. Both in boys were presented with the blue line. And girls, BMI was associated with their weight dysanapsis, both BMI as a continuous variable and overweight or obesity. And Moreover, dysanapsis was associated with severe asthma exacerbations in kids with asthma. So this would be also a nonallergic mechanism, another structural defect, if you will. So where are we going with all of this?

So we currently have several projects. One is to look at social epigenomics. This was called by DNA. I didn't make that up-- that name. So we're doing a study of exposure to violence and the methylone, the genome-wide DNA methylation, in airway epithelium among white blood cells for Puerto Rican children, to see whether this violence-related methylation marks, if you will, are also related to asthma. And that's morbidity. The second thing that we're doing is, we are enrolling kids with asthma, taking nasal samples, and seeing where we can develop nasal markers that predict response to inhaled steroids in these kids. Kid comes in, we take nasal samples, we followed them for six weeks. They had never received steroids, they get steroids. And there you have it.

And the next thing to do and if I have enough time, is to do a study of newborns, where you would collect nasal samples and follow them over time to see if you can predict the development of A2B in asthma. Which is the million dollar question in pediatric pulmonary allergy, right? Because most kids always will not go on to develop asthma. So if you only knew. And that's the next step. And finally, people ask me all the time, how about this? Of course, the time is right for clinical trials of a stress reduction. There are also evidence with depression. I didn't show you that. Depression treatment, weight loss in asthma in at least adolescents. So it takes me back to health disparities in asthma.

Five years ago, I was very proud to be a founding member of the Health Equality and Diversity Committee of the American Thoracic Society. And we've had a series of publications on the field. This is the first one, which is an opposition statement, showing that really, 95% of disparities are a very large proportion as explained by environment. And some of these are very familiar to you. Tobacco smoke, air pollution in adults occupational hazards is becoming more and more evident-- drug use-- and obesity. There's an epidemic of obesity in this nation. And that's associated with sleep disorders and asthma.

So how do you tackle a problem as complicated? Well, this is what we propose. You have to have [INAUDIBLE] advocacy, an advocacy that starts in your community, the local level, state national levels is long course. For sure, environmental justice-- we have a very active environmental health policy group. We have an office in Washington that advocates for clean air and other things. Implement, of course, excellent health care, which is what you do all in this audience. Promote a healthy lifestyle-- but at the core of this is innovation and research.

So how can you improve asthma care? So I'm going to share some very, very simple data. There is at this point overwhelming evidence that increase on appropriate prescription, an education on how to using health corticosteroids by PCPs, has a positive impact on asthma management and reduction of health disparities, while also reducing cost. It's been shown multiple times in several cities in the US and across the world. So I'm going to show you data from Costa Rica.

So it turns out that my colleague, Manuel Soto Quiros, recently retired. He was the Chief of Pediatric Pulmonary at Children's Hospital in San Jose, Costa Rica. He started a national asthma campaign in 2003. Granted it's a small country, they have universal health care, which we're still dreaming of. This was kids and adults even though he was a pediatrician. So he had a lot of support from the government. And one of the very first thing that was done prior to 2004, only a specialist could prescribe inhaled corticosteroids in Costa Rica. In 2004, [INAUDIBLE] was released to all PCPs.

What happened after that? These are temporal trends. And here again, you have data for kids and adults. These are data from hospitalizations. And look how they've decreased. It was a dramatic reduction in hospitalizations. My colleague, Michelle Cloutier, showed the same thing in Hartford, Connecticut, which is the poorest city of its size in the US Northeast. She started a campaign called, Easy Breathing for pediatricians and family practitioners to increase use of inhaled steroids, a very simple sheet that PCPs check. They get to the end and if things check out, they prescribe inhaled corticosteroids.

Prescriptions of inhaled corticosteroids went from about 15% with Easy Breathing, the campaign that started, to 95%. During that time period, hospitalizations were reduced by 20%. Mind you, that's a city that's almost populated exclusively by African-Americans and Puerto Ricans. Yes, one of the largest burdens of asthma in all of the US in kids. So it works. So this is a complicated problem. And over the last two or three years, you hear these increasing statements about preserving the start of school and going back to the past. And people tell us that this is unsolvable.

In 1999, Elie Wiesel, who's a Holocaust survivor, gave a speech at the White House called, The Perils of Indifference. Mr. Wiesel started by saying that indifference is a strange and an unnatural state, being which the order becomes an abstraction. For the person who is indifferent, the neighbor is meaningless. Indifference blurs the lines between light and darkness, cruelty and compassion, good and evil. And indifference is what's caused these problems. This problem can, of course, be solved.

Do not tell me that the country that overcame the Great Depression, who played a role in winning two World Wars, and who put a man on the moon cannot give good health care to all of its citizens, regardless of socioeconomic status or skin color. Do not tell me that. For in the words of Lyndon Baines Johnson, this is what America is about. It is uncrossed desert and the unclimbed ridge. It is the star that is not reached and the harvest sleeping in the unplowed ground. Is our old world gone? We say farewell. Is a new world coming? We welcome it and we shall bend it to the hopes of humankind. We can do this. Thank you very much.

[APPLAUSE]