Hormone Therapy:
A Special Interview with Sylvia Wassertheil-Smoller
By Dr. Joseph Mercola

DM: Dr. Joseph Mercola

SS: Sylvia Wassertheil-Smoller

DM: Hormonal supplementation, especially in the post-menopausal age for women, is a relatively controversial subject. Hi, this is Dr. Mercola, helping you take control of your health. Today we are joined by Dr. Sylvia Smoller, who is the principal investigator of the Women’s Health Initiative (WHI), which you may know and recognize as one of the largest studies ever done at examining this issue. It probably is the largest study. It was started in 1991 and looked at over a 160,000 post-menopausal women in 39 clinical centers. Dr. Smoller is a member of the staff at Albert Einstein College of Medicine. She is here today to help us unravel some of the confusion around this topic.

Welcome and thank you so much for joining us today.

SS: Thank you. It’s a pleasure to be here.

DM: You’re an authority in epidemiology and in really teasing out the details of some of the confusion in this area. Maybe you can give us some more information about yourself professionally, because it’s always helpful to have a framework to understand what the information you’re going to be sharing with us, then why you got interested in this, and maybe what led to you being the principal investigator of this important study.

SS: Okay, great. I’m a professor at the Albert Einstein College of Medicine in the Department of Epidemiology and Population Health. Most of my career has been doing population-based studies, either observational studies, where you follow a group of people over a long period of time and see what factors predict events happening (which are risk factors and which are protective factors), as well as clinical trials which test…

Clinical trials are sort of the gold standard in our field. The Women’s Health Initiative included a few clinical trials. One of which was a clinical trial for hormone therapy for post-menopausal women. It also included an observational study, a diet clinical trial, and so on, which I hope to tell you more about.

DM: Well, that’s great. We really want to focus on the hormonal component. Maybe you can provide us with the context of these studies and what led to the development of this massive trial that was done, and my guess is still in progress, right? They’re still collecting data?

SS: We’re still collecting data. The trial itself is completed, but we’re still following all the women who enrolled in that trial and who gave their consent to be followed. It’s still on going. Well, your question: what led to this? It’s really very interesting. When I started out in this field, it was really a boys’ club. Women’s health was not in the front of anyone’s mind actually. In fact, women did not participate in studies of health problems nor were they in leadership positions. Of course, these two things are not unrelated.
It was thought of that, first of all, women do get heart disease about 10 years later than men. I don’t know whether it was to “protect” women or because people didn’t think that heart disease was an important thing for women. It was really ignored for many years. Everything we knew about heart disease really came from studies on men. Now, women did play a role. Because women did get heart disease about 10 years after men did, somebody said, “Ah, Eureka! It must be their hormones that protect them.”

DM: That was the thought in the ‘80s and the ‘90s, early ‘90s.

SS: That’s right. Well, even before that, someone said, “Oh, it must protect women, therefore it should be good for men.” They did something called the Coronary Drug Project, where they gave men estrogen, men who were at a high risk for heart attack. They gave them estrogen to see if they can protect them from these heart attacks. Of course, that was a disaster, because men did not like grown breasts and other side effects of hormones. But also, they were dying at a very high rate. They were getting quite high doses of estrogen. It turned out they were really dying from heart attacks. They abandoned that for decades. They abandoned the thought of hormones.

And then it became apparent that everyone thought hormones were protective and that it was time to do a clinical trial. That’s how the Women’s Health Initiative really began. By the way, nowadays, when you apply for a grant at the National Institutes of Health (NIH), you have to indicate what proportion are women. If it’s too small a proportion, you often may not get funded. Of course, you don’t do prostate cancer trials on women, so that’s not an issue.

DM: Sure. Yes. And for those of our listeners who don’t know what NIH is (a small percentage might not know), that’s the National Institutes of Health, clearly the primary funder, if not the sole funder of the Women’s Health Initiative.

SS: It was the sole funder although Wyeth Ayerst, who made the hormone pills, contributed the pills as well as the placebo pills that looked just exactly like the hormone pills.

DM: Interesting. Was that trial just estrogen or estrogen and progestin?

SS: It was really two separate trials, you could say. One trial was estrogen alone for women who have had a hysterectomy versus placebo. Because women who have had a hysterectomy could take estrogen alone, but women who still have an intact uterus had to take estrogen plus progestin to protect their uterus. The other trial was estrogen plus progestin versus placebo for women who did not [have hysterectomy].

DM: Thanks for that clarification. If I could jump in… I mean, we’re going to get into the details of this study because I think it’s going to really provide us with a lot of valuable information. Who better to get it from than the principal investigator? Clearly, it’s an unequivocal established fact that women are relatively protected from heart disease. I mean, that’s uncontroversial. Your study was done to tease out some of the details. But I’m wondering if you can give us your current answer in 2015 what the protective effect is as a result of.

SS: Let me just say it’s not exactly the case that women are protected from heart disease.

DM: Oh, okay. That’s the confusion. I’m confused.

SS: Well, in fact, the number one cause of death among women is heart disease.

DM: But isn’t that later in life? I mean, don’t they have this relative protection while they’re still menstruating?
SS: If they’re still menstruating, they have a much lower rate of heart disease. It is certainly true that they do get heart disease, as I said before, about 10 years later than men do.

DM: Right. That’s the effect I was seeking to tease out the details on, what was responsible for that observation.

SS: Right. Well, it was an observation, and of course, people thought that it was the hormones that were protective. It might have been that the hormones are protective earlier in life.

But the point is that replacing those hormones once they’re no longer being manufactured by the women, in fact, did not protect women from heart disease. It caused more strokes, more dementia, and more breast cancer in women who are taking estrogen plus progestin. Women without a uterus who are taking the estrogen alone had a more favorable profile. They still got heart disease, but it wasn’t that clear that it was the estrogen that was responsible for it. They actually had a little bit less breast cancer, but they still were at high risk for stroke and dementia.

DM: I’m seeking to understand what was responsible for this relative protection that menstruating women seem to have. There are some researchers who believe that it’s this monthly loss of blood (which obviously contains iron), lowering the iron level in the body, which serves as a prooxidant or an anti-antioxidant to cause much oxidative damage in the body. I’m wondering if you have any comments on that.

SS: That’s certainly probably a good part of it. I think it may be other mechanisms at work as well. I mean, estrogen earlier on in life may be somewhat protective. But the iron hypothesis is one that’s pretty well established. I think that that’s certainly partly true. But there are all kinds of different things that go on in a woman’s body when she’s still menstruating, and it’s the balance of the various hormones, the balance of estrogen, progestin, and so on.

DM: Let’s get back to the study and tease out some of the details. As you had mentioned, there were two arms of the trial or the initiative: 1) supplementing estrogen in women who did not have uteruses and 2) the women who did have intact uteruses, they were given estrogen and progestin. Both you and I said “progestin” not “progesterone.” Progestin is the synthetic progesterone; it’s not natural progesterone.

The standard of care at the time the study was started in 1991 clearly was to provide estrogen replacement therapy (ERT). In fact, I was hired by, I think it was Ayerst, as a professional speaker in the late ‘80s, mid to late ‘80s, to go around the country and lecture physicians. I was a paid speaker to lecture physicians about the benefits of estrogen replacement therapy, because I believed in it. I bought it hook, line, and sinker.

[----- 10:00 -----]

But there were some interesting results that came about. It’s the findings in your study that really turned this standard of care on its head. Why don’t you discuss what you found in those years of study? I mean, literally, it was massive. It was just a huge shift in the whole thinking on this topic.

SS: It was absolutely massive, and it was such a surprise to all of us because, you know, this was double blind. The investigators and the patients did not know whether they were getting the placebo or the active hormone pill. We were shocked because we really expected that this would come out to show a good deal of benefits. I think everybody was really surprised, as well as the stock market, by the way.

DM: Yeah. That’s usually connected in some way.
**SS:** Yeah. It was really a very big surprise to all of us. The first trial that was stopped early was the estrogen plus progestin trial. That was stopped in 2002, close to two years before it was supposed to stop because the results were so dramatic.

These trials are monitored by a safety monitoring board that’s not connected with the study, but that gets access to the data and monitors it for either harm or benefit. In this case, the results were so clear to them that they advised NIH to stop this trial so it was stopped. There was an enormous amount of publicity about it.

**DM:** Oh, enormous. That was 13 years ago. Many people watching this might remember. It was on the front page of every major media publication and the leading headline story in all the news. It was just massive. One of the biggest exposures on any medical topic that I can recall.

**SS:** One of the rare cases in medicine where the weight of evidence, which had come from observational studies in the past, was really strong for protective effect. And Prempro... By the way, you also asked about progestin and why we used that particular formula, because Prempro was the thing that was most prescribed for women. That was the pill in the United States that millions and millions of women were taking, so that was the pill that we tested.

**DM:** Sure. And there are reasons for that. The reason it was the most common has to do more with monetary issues than the reality of seeking to identify an ideal hormone replacement, but that’s another topic.

**SS:** That’s very complex. But in any case, that was the one.

**DM:** And it makes perfect sense. Why would you want to test something that women aren’t using?

**SS:** That’s right. When that trial was stopped, the other trial (the one for women who had uterus) continued. But let me just get back for a minute to why we all thought there was a protective effect. That came from all these years of observational studies.

Now, I want to make this distinction between an observational prospective study and a clinical trial. In an observational prospective study, women who take hormones and those who don’t take hormones are observed over a period of years. We look to see how many events, how many heart attacks, and how many breast cancers happen in each of these two groups. In a clinical trial, women are randomly assigned to either take the hormone or take a look-alike pill that’s really a placebo and has no active ingredients in it.

Why is that a better test? Because in an observational study, the women who take the hormones are different from the ones who don’t take the hormones. They tended to be less obese. They exercised more. They ate healthier foods. They were in many ways more health-conscious and healthier to begin with than women who were not taking hormones. That’s what skewed the results. But in the clinical trial, you get rid of that kind of bias. It’s a random assignment. It’s a much higher standard of proof.

**DM:** Let me just interject here, and thank you for that explanation. The one-sentence summary of that that is commonly thrown around nowadays, which your explanation brilliantly describes, is correlation does not equal causation.

**SS:** Excellent. That’s exactly right.

**DM:** I’m sorry I interrupted you. You can continue. I just wanted to make a...
SS: Right. An association doesn’t mean a causation. You don’t know what direction things are going. Anyway, I think…

DM: A classic illustration. Everyone thought this was the case. That’s why all these women were on it. They were being harmed because they confused correlation with causation.

SS: That’s right. Also, there’s something very appealing. I think the slogan was “Feminine Forever.” It was very nice. I think women and physicians all thought that you really could retard aging and you could remain vibrant, feminine, and wrinkle-free, and that it would just do wonders for simply every part of your body if you could only continue on having these hormones. But you know, nature didn’t intend it that way. There’s a reason why women stop menstruating after a certain period of time.

DM: All right. After 2002, it became a well-established fact. The standard of care became reversed. It became almost criminal to prescribe progestins for women in hormone replacement therapy. They had a big black box and still to this day, a big black box warning on the progestin. They’re still available.

SS: That’s right.

DM: Have you teased out some of the details of the mechanism as to why there was such a severe adverse effect and increased risk in heart disease and cardiovascular complication?

SS: We’re looking both at genetics, blood biomarkers, and at all kinds of things to elucidate the mechanism. I think it’s still elusive. I think we still haven’t quite found why this is happening. By the way, we don’t call it hormone replacement therapy, at least the people in the women’s health center.

DM: Okay. I apologize.

SS: No, it’s okay. But we call it hormone therapy.

DM: Hormone therapy.

SS: Because what are we replacing? We’re not replacing.

DM: That’s the conventional name given in the literature.

SS: Yeah.

DM: So that’s what I was…

SS: That’s right. But we’re trying to change that. We’re trying to just refer to it as hormone therapy.

DM: Sure. That makes sense. So, have you or your team or other investigators looked at… I know this wasn’t part of the trial. But the obvious question, especially to our audience would be what would happen in they used natural progesterone, the same hormone that the body naturally produces, not the synthetic one with all the complications?

SS: Some people have said that that might do better, but we have no evidence for that. We can’t do another trial…

DM: Imagine that.

SS: For every kind of preparation that’s out there. There is a point at which we have to draw inferences. We do know it’s not protective. It does not protect you from heart disease, stroke, or breast cancer.

DM: What’s not protective? The synthetic progestin?
SS: The combination of estrogen plus progestin. Estrogen alone is not protective for stroke, dementia, or many of the other things that happen to women as they age. We know you certainly shouldn’t take it to prevent disease. That’s what the hope was initially. That this will prove to be a far preventive measure, but it isn’t. That’s very clear on the labeling: hormones should not be used to prevent heart disease, dementia, or stroke, particularly stroke, where it really is a big risk factor.

DM: Now, this was clearly the well-established standard of care prior 2002.

SS: Right.

DM: Changing the standard of care in any discipline, certainly in medicine, is like trying to turn the Titanic.

SS: Absolutely.

DM: It’s a slow shift and change. I’m wondering if your network and the meetings that you attend discuss the issue of how many physicians are still prescribing this well-proven detrimental effect.

SS: The prescriptions went down by something like two-thirds when these news were first released, but as you say, it’s very hard to change a behavior and to change conceptions and attitudes towards things. There was definitely a backlash. Particularly many in the OB-GYN community said, “Ah, you were giving them too late. If you gave them just at the time that the woman was perimenopausal, that would be protective.” We didn’t find evidence for that in the estrogen plus progestin group.

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DM: Yeah. The same argument can be used for the use of statin drugs to prevent coronary heart disease, the relative versus absolute risk. Maybe this looks like a large number, but the reality is it’s a very tiny number. The benefits are clearly outweighed by the adverse effects.

SS: Right. And you know, the thing is that even though it’s a small absolute number—and I did this calculation as did others at WHI, but I’ve forgotten it. I could look it up. Even though in absolute terms, it’s a small number, the fact is that when you multiply that by the number of post-menopausal women and the number who are taking these pills, it translates into millions of lives saved by not taking them.

DM: Yes. Really, it’s an important piece of information that you teased out through your hard work and efforts. I mean, decades. That’s one of the benefits of this format. We’re able to connect with researchers like yourself who have pretty much committed most of their professional life to uncovering these truths.

SS: Right.

DM: It’s so sad that there’s still a significant percentage of physicians who don’t believe it and who are allowed legally to prescribe this and hurt women as a result of their ignorance.

SS: One of the things is that, particularly OB-GYN physicians, they see women who have very severe menopausal symptoms. They don’t see the general population; they see a very select group of women who come to them and say, “Oh, I’m really suffering. I have these dreadful symptoms of menopause.” They have a slightly biased view of who is taking these pills. And maybe for someone who is really
severely suffering, a small dose for a short period of time might be appropriate. But what happened with
the hormones is that everybody was taking them.

You have a little discomfort. Listen, I went through menopause. I had a little fan that I used to have on my
desk. People came in, and they said, “What is this?” I said, “Well, I’m perspiring.” And it passed. It
certainly wasn’t worthwhile taking the risk to have a little less discomfort, and that discomfort did pass.
Although with some women it can be severe.

DM: And clearly, the estrogen and potentially progestin combination will be effective at relieving those
symptoms, but it’s only a Band-Aid. It doesn’t in any way, shape or form, address the cause of that. There
are far safer therapies to address that, which are effective.

SS: Right.

DM: And which are not going to cause this massive increase in cardiovascular disease.

SS: That’s absolutely right.

DM: Now, let’s talk about the estrogen, because the estrogen was provided to the 160,000 women by
Ayerst, and it was Premarin, which is conjugated equine estrogen (CEE). For those who don’t know what
that means, that means they were extracted from mare’s urine. They’re not human estrogens; they’re
horse estrogens, essentially. They’re not the same. I’m wondering what type of analysis went into the
differences there. Because there are three different types of estrogen: E1, E2, and E3. I think... I’m not
sure. They’re comparable equivalents. They’re not the same. The ratios are quite distorted in horses’
urine.

SS: There are many different kinds of estrogens, and you’re right, this is one kind. By the way, they
didn’t provide Premarin for the 160,000 women; only for the women who are in the trial.

DM: Okay.

SS: There were 27,000 women in the hormone trials and about 10,000 in the estrogen alone trial. That’s
what was done there.

DM: Okay.

SS: The picture is more nuanced with the estrogen alone. And first of all, let’s remember these are
different women. They are heavier on a whole. They have a different risk profile. Other things happen to
them. They have higher rates of heart disease in any case. They’re different, demographically speaking.
But the picture of estrogen alone is a little bit more nuanced.

For example, we didn’t find the really bad adverse effect of breast cancer in women taking estrogen
alone. There was even a hint that it was protective. We didn’t find much difference in heart disease. We
still found a big difference in stroke and dementia, and that’s very worrisome. I mean, I think one of the
things that people are most afraid of is stroke and dementia because it leaves you so debilitated.

DM: Oh, absolutely. It’s really a challenge, maybe not so much for you, if you lose your mind, but
certainly your friends and relatives.

SS: Yeah. Well, I don’t think you’ll lose your mind. I think there’s a long period where you’re aware.

DM: Sure.
SS: It’s quite horrendous. And I think the other thing is if you have some treatment for cancer that causes side effects and risks, you might take that chance because the cancer itself is such a terrible thing. But if you have that kind of treatment for a common cold, like I just had, you wouldn’t want to take that risk. You know that cold is going to pass and go away, and it’s not life-threatening.

DM: Absolutely.

SS: You’re willing to take different risks depending on what it is that you’re treating. A woman has to weigh, is it worth taking this chance to relieve perspiration or to relieve vaginal dryness? Like you said before, there are other things you can do.

DM: Absolutely. We try to keep it as safe as possible. It sounds like there was really no further investigation as to the different types of estrogens.

SS: You have to infer. In other words, you have to just make a leap because it will not be another clinical trial of this magnitude, testing other preparations.

DM: Yeah. I’m not sure the average person listening understands what type of a massive process it was to put this trial together. There are only a handful of these that were ever done, ever. You just don’t do this every other week.

SS: It was enormous. But you know, the remarkable thing is that women who participated in this study were so committed, so loyal to it, and so happy to participate that it’s one of the studies where we had one of the highest adherence and follow-up rates. And most of them are still willing to be followed and to contribute to the knowledge about this. It was really a remarkable group of 160,000 women.

DM: Yeah, it’s really great.

SS: They made it fun for all of us.

DM: Now, as part of that intervention trial, was there something done with multivitamins and mineral use, especially in women with breast cancer?

SS: Yeah, not in this trial. That came from the observational study.

DM: Correlation is not causation, so we just prophesized that.

SS: That’s right. Correlation is not causation. Nevertheless, it’s better than what we call case-controlled studies where you take people with the disease and without the disease and then you look backwards to see who did what. That’s flawed with all kinds of potential biases, which we try to control for statistically.

But in this prospective study, there were about 100,000 women who participated in it, and we had all kinds of information on them, including blood, DNA for genetic studies, questionnaires, and all kinds of things. Now, in that study of 100,000 women, which is massive, we looked at the rates of cancer and cardiovascular disease in women who took multivitamin supplements.

[----- 30:00 -----]

And in fact, we found on average, no difference in the incidence of these diseases. We then looked separately at women who were already diagnosed with breast cancers. So they were breast cancer survivors. We found that multivitamins with minerals, which is the preparation that most people take, actually protected against mortality from breast cancer.
Also, once you have the disease, taking these multivitamin and minerals appeared to be protective against dying from the breast cancer. Now, usually things that are protective like that are also protective in primary prevention. It is in preventing getting that breast cancer to begin with. In this case, we didn’t see that. But nevertheless they definitely – no matter what we did, no matter what we controlled for, no matter how we looked at the data – still showed a benefit in terms of dying from breast cancer.

**DM:** Was there a lot of negative feedback from other physicians who were investigating?

**SS:** None on that. No, none on that.

**DM:** Okay. That’s interesting.

**SS:** You know, there are fads in these things. I want to caution against people taking too much.

**DM:** Sure.

**SS:** Because that has its own dangers. But mostly people would take one multivitamin and mineral pill a day in the group that we studied. That did seem to be protective from dying from breast cancer and all-cause mortality as well.

**DM:** That’s an interesting observation.

**SS:** Yeah. We want to follow that up by looking at other cohorts to see how broadly you can generalize.

**DM:** What would’ve been nice is – I don’t know if you did this, but the tools for it weren’t readily available when you started this study in 1991. But vitamin D level has been shown by many studies to have clear correlation with breast cancer. I’m wondering if there’s any effort to tease out that detail.

**SS:** Yes, there is. There have been a lot of papers in WHI in vitamin D and its effects. It’s not so easy because vitamin D is also synthesized by the sunlight. People living in different regions get different amounts of vitamin D. You have to factor all of that in. But I think it’s fairly well accepted that vitamin D is protective and that many, many women have too low levels of vitamin D in their blood.

**DM:** Yeah, most likely the majority. It’s just like diabetes or high blood pressure.

**SS:** Right.

**DM:** You’re not going to know what your vitamin level D is. You have to get it measured. There’s just no way. You’re going to have the symptoms of it until it’s too late.

**SS:** Other nutrients… It’s hard to look at single nutrients because we don’t eat nutrients; we eat foods, and foods have all kinds of things that interact with each other, that are in different proportions, and so on. It’s hard to look at specific nutrients unless there’s a big deficiency of them. One of our latest studies showed that potassium, dietary potassium is protective against stroke. We’re now looking to see whether it’s protective against dementia as well. The recommended daily allowance of potassium is something like 4,700 milligrams…

**DM:** Which is nearly five grams. That’s almost a teaspoon.

**SS:** Nearly five grams. That’s by our Department of Agriculture. The World Health Organization (WHO) has a slightly lower recommendation of about 3,500 milligrams per day of potassium. But very few people get that. In our study, only about 16 percent got more than 3,500 milligrams.
DM: Yeah, I was just going to make a comment on that. Because anyone who has done a dietary analysis – and there are some really great tools that you can do online, they are free, and you carefully enter all the foods you eat – you’ll see really quickly how hard it is even to get above two grams a day of potassium. The caution here and I’m sure you looked at it was this was dietary potassium; it wasn’t supplemental potassium.

SS: No, it’s not.

DM: A pill that people were taking.

SS: There is a problem with supplemental potassium because, for instance, people with kidney disease. Many people have beginning kidney disease that they’re not aware of. Too high a potassium can be very dangerous. So potassium supplements, you shouldn’t take them without talking to your doctor definitely. But you know, it’s not that hard to get adequate potassium in foods because so many foods have potassium. Certainly vegetables and fruits…

DM: The good healthy foods do, but the foods people wind up eating have relatively small amounts. That sodium to potassium ratio, in which sodium is so high in processed foods, that’s a really powerful predictor of how healthy you’re going to be.

SS: Yes.

DM: As your studies bore out.

SS: That’s right. You can get potassium in bananas, avocados, oranges, apricots, meats even, and yogurt. It’s not that hard to get it in adequate [amount].

DM: Well, you have to be conscious. You really have to… I mean not necessarily seeking for potassium, because if you’re seeking out healthy foods, you’ll do it. But it just doesn’t happen willy-nilly. The average person, as you said in your study, 16 percent were not even getting 3500, which is not the five grams or the 4,500 milligrams that we’re talking about.

SS: Well, I think something like three percent got 4,500.

DM: So yes, it’s not hard, but the practical reality is it is hard because most people aren’t doing it.

SS: That’s true.

DM: It has to be a compliance issue. People just don’t like to eat… It’s not as tasty necessarily.

SS: Well, I think it’s…

DM: Well, for some people, you know. If you explain…

SW: Being habituated to eating.

DM: Right. So, the other thing you looked at was your waist circumference, body shape, and waist to hip ratio. I’m really interested in what you found in that, specifically comparing the differences in waist to hip ratio, which is a bit more challenging to calculate than waist circumference, but from my review, seems to be a better indicator and predictor. I’m wondering what your finding’s for it.

SS: I think they are better predictors than body mass index (BMI). Waist alone is not a bad predictor. Waist to height is better, but waist alone is not a bad predictor all by itself. In fact, in another study we’re doing called the Hispanic Community Health Study (HCHS), someone has just written a paper comparing
all of these measures: body mass index, waist to hip, waist, and few other metrics of body size and body composition. They found that they’re all fairly good with maybe the waist to hip being the best.

But one of the issues with body mass index is that women – men also, but women probably more so – lose height as they age. Body mass index is weight in kilograms divided by meters squared. If you lose height, your body mass index changes, but it may not be in the same proportion that’s related to risk.

The other thing that we found in some of our studies (some of our group has been looking at that) is what they call “healthy obese,” metabolically healthy obese. They are people who are obese and overweight who are metabolically healthy. Their insulin levels, their glucose levels, their cholesterol levels are all okay. We call those metabolically healthy overweight or obese.

Then there are people who are lean but are metabolically unhealthy. Even though they are thin, they have bad cholesterol profile, they have insulin and glucose problems, and so on. These are the lean, metabolically unhealthy. Then there are the obese, metabolically unhealthy and the lean, metabolically healthy. There are at least four groups.

Among the obese, most people are metabolically unhealthy. There is this smaller group that is metabolically healthy. Some people have shown that if you’re overweight and metabolically healthy, eventually you’ll become metabolically unhealthy. It’s an extremely complex situation, but the bottomline is it’s the metabolism that counts. That’s partially influenced by genetics as well.

DM: Was evaluating exercise or movement strategies a component of your trial?

SS: We have questions on physical activity – leisure physical activity, work physical activity, and so on. These are all self-reports.

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They have shown what we expect them to show: more exercise helps with everything. Again, in the Hispanic Community Health Study we have more direct measures of exercise. We have something called the Actical, where people wear these devices and tell us exactly how much physical activity they are getting.

DM: Like a fitness tracker?

SS: Yes, something like that. But the self-report in the Women’s Health Initiative is definitely predictive of the more exercise, the better health. One other interesting thing that we’re finding (and people are writing papers about this), is sedentary behavior independent of physical activity.

DM: Oh, please enlighten us on that because that’s really one of the hottest topics in health today. What were your findings?

SS: It is. What we found is that sedentary behavior is associated with cardiovascular risk and cardiovascular diseases. This is apart from the amount of physical activity you get. You could go out to the gym and get your physical activity, but then you spend six or seven hours a day sitting, and that is a risk factor.

DM: I was guilty of that. I was incredibly fit almost all my entire life cardiovascular-wise. I was exercising an hour a day, yet I was sitting for over 10 years. The average person sits eight hours a day, by the way. But office workers can sit up to 13 hours a day, and I was probably closer to 13 to 15 hours a day sitting. That just devastated my health. Now, I sit… I think if you can sit less than three hours a day, it’s much better.
SS: It’s very hard to do that for people who work in basically sedentary occupations. I find I’m sitting all the time in front of my computer.

DM: Well, it’s not as hard as you think. It’s just… It’s like when we talked about getting the extra potassium. The big shift is just to stand up. Dr. James Levine, he’s a researcher of Mayo Clinic, has done that. He actually serves as a consultant in many Fortune 500 companies to get them to get stand-up desks. When they do that, the work performance improves and the profits of their corporation increases. It’s a really good return on their investment and the health of their employees.

SS: Oh, that’s wonderful.

DM: Simply standing up.

SS: I have a colleague who has that. He has a computer desk that’s at a stand-up height. He stands and works standing up.

DM: Yeah. I think eventually there’s going to be this transition. Just like when you did your study in 1991, it was well accepted that hormone therapy was useful for women. And 10 years later, you found out it wasn’t, or 11 years. But now we’re going to find the same thing with this sitting and this is going to be… It’s just tragic in my mind that we force kids to sit down in school. It’s like, “Oh, my God, a prescription for disaster.” It’s not what they’re designed to do.

SS: But, of course, they have recess, which is terrible.

DM: It’s like the exercise versus sedentary. You know, 95 percent of it is sitting down versus the five percent getting up.

SS: The thing is if you can’t work standing up, which I’m going to try even though…

DM: Oh, I couldn’t encourage you more. It’s a simple transition. Do it slowly. You can even experiment. Get something to raise your monitor. If you have a notebook, you can easily take a garbage can, put it upside down on your desk, and use that as a platform so your investment is close to zero. And then you’re set. That’s what I do when I go travel in a hotel, because I typically sit less than a half hour a day.

SS: Really?

DM: Yeah. It just changed my life. I had chronic back pain, and it just disappeared once I started doing that. It’s just incredible. There are 10,000 studies that show this. Metabolically, it’s a massive change just from standing up. Just from standing up.

SS: You’re really inspiring me. What I had started doing is to get up every hour.

DM: Yeah, I tried it. I was getting up every 10 minutes.

SS: Wow.

DM: And it didn’t work. I was stretching, moving, and doing these exercises. The only thing that fixed it was standing up. It was for me personally. I’m sure standing up six times an hour is going to be better than sitting down. But I just think do it all, go all out, get a stand-up desk, and change your life.

SS: It’s very inspiring.

DM: Yeah. I didn’t realize that was a finding in your study. Not surprising, but it’s really encouraging to find that out.
SS: Yes, it is. The Women's Health Initiative has been just a wealth of information and knowledge in health. Just a wealth. We have a few ancillary studies that are ongoing. For example, we have something called the Long Life Study (LLS), where we paid a home visit to women very recently actually, a couple of years ago, to about 7,000 or 8,000 women who were over the age of 70. We’re going to see what factors protect and are helpful in later life. We have something called Life and Longevity After Cancer (LILAC), which is a study of breast cancer survivors. There are all kinds of things that are coming out of the Women's Health Initiative. And, of course, all our genetic studies.

DM: Sure, absolutely.

SS: It’s a great investment of taxpayer dollars.

DM: Yes, indeed. Maybe you can provide us some of the highlights. We talked about sitting, which your study supports. But maybe summarize all the important insights that this investment of tax dollars, US tax dollars provided, so that women can actually improve their health and stay healthy as they continue to age.

SS: It’s very hard to summarize. We have over 2,000 papers.

DM: That’s all?

SS: Really, it’s awesome. It’s very hard to summarize, but I mean…

DM: Well, the highlights.

SS: The highlights, we’ve already discussed the hormone issue, right? One of the things, you know. There was another trial called the Dietary Modification Trial that included 48,000 women. We wanted to see whether a low-fat diet would lower the risk of breast cancer. Now, it was low any kind of fat specified that it should be saturated or unsaturated. Unfortunately, not all trials come out with definitive answers as the hormone trial did. We actually found no difference in breast cancer rate among the women who were on the low-fat diet versus those who were on the regular diet. Nevertheless, we’re learning things from that study.

Then there was a calcium and vitamin D trial where we gave calcium and vitamin D supplements versus placebo. Here, we found a little protection for colorectal cancer.

But you want to know the highlights of the findings. There were lots of findings in the observational study. We talked about the multivitamins. We talked about potassium. One of the studies that we’ve recently published had to do with mammograms. There’s a big push now to have women after age 75 to stop having mammograms. I don’t know if you’re aware of that.

DM: Sure, absolutely.

SS: We actually showed that women after 75 should have mammogram because it saves lives. That was, I think, a highlight. What else can I say? Like I said, there are 2,000 papers. It’s a little hard to…

DM: Sure. I think you’ve given us many good insights. We really all appreciate the hard work and effort you’ve done and continue to do in teasing out these details because, as you mentioned earlier, these types of trials are few and far between.

SS: Beautiful.

DM: So it’s important to make the most of them when they’re done.
SS: Absolutely. But also the observation… Even though, in the case of hormones, the observational data before the trial prove to be incorrect, we can’t throw out the baby with the bathwater, because there are many, many things that cannot be investigated in clinical trials that you need observational studies for. And they’re very useful. We’ve got a ton of information from our observational study.

Oh, here are some additional highlights: something that’s really very common and that’s depression. We’ve done a whole bunch of studies looking at depression as a risk factor. We found that, yes, indeed… We’re not talking about clinical depression, where a psychiatrist evaluates a patient and says, “You’re clinically depressed”; we’re talking about depressive symptoms that we measure on a scale, which are predictive of depression but are not the same thing, but they’re high depressive symptoms.

These have been shown to be a risk for stroke, a risk for all kinds of conditions or diseases, and so on. What are some of the things that can alleviate that and that we also found important? Social supports. Loneliness is a risk factor. All of these we found from our observational study. Social support, belonging to a group, getting out there, and having involvement in life, all are protective. So again, we found this from observational studies.

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We also did a study on… Of course, we’ve done lots of studies on high blood pressure. Now, we’re looking at what about controlling blood pressure in the Long Life Study in older people. We’ve got a ton of information from the observational studies. We shouldn’t downplay it because it’s really good.

DM: No, they’re although correlation doesn’t prove causation, but you can still get valuable insights and prediction as to what might be useful. If there’s some controversy, you can secure and get a funding to test it.

SS: That’s right. And also, there are many ways to minimize the biases inherent in a prospective study. One of them is called – I don’t know if you’re interested in hearing this – propensity analysis. For example, we did a study on antidepressant drugs, which is very hard to tease out from the depression itself. But the first thing we did was we calculated the propensity to be on a drug. How likely is a person based on their other characteristics – their demographic, their other conditions, and so on – would likely to be on the drug?

We then controlled for that when we look at the comparison of those who are on the drug versus those who weren’t. We controlled for the propensity to be on the drug. That’s one technique for trying to get rid of the biases inherent in prospective studies rather than clinical trials. But I should point out, and I failed to do that earlier on, that the psychological dimensions are very, very important in health. We’ve gotten a lot of data from that.

DM: I think that’s important. Data is typically not emphasized a lot.

SS: It’s not.

DM: We’re looking at pharmacological interventions or lifestyle, but that is a massively important variable. There’s no question.

SS: Not only that, depression is a stronger risk factor, as some other things as high cholesterol, for example, or smoking.

DM: Smoking, right.
SS: It’s really a strong… Well, smoking is a very strong risk factor. Hardly anything beats that. But it’s as important as some other risk factors that we commonly accept. But no one pays attention to it. I mean, when you go to a doctor, it’s very unlikely that he or she who’s seeing 30 patients in an hour is going to ask anything to do with depression, and yet it’s a strong risk factor. Fortunately, the American Heart Association (AHA) has recently recognized that as a risk factor among people who have heart disease. It’s getting recognition, but we did a lot of work on that in the Women’s Health Initiative.

DM: Well, many people fail to realize that it has a terminal side effect, which is suicide. And 30,000 people a year, every year in the United States alone commit suicide. Obviously, that’s extreme depression, but nevertheless, that’s a lot of people.

SS: That’s a lot of people.

DM: That’s a hundred people every day, every day in United States alone that commit suicide.

SS: That is amazing. But also it has more subtle effects that lead to heart disease. A colleague of mine actually at Harvard is an expert on triggers. Murray Mittleman is his name is. He’s an expert on triggers of heart attacks, strokes, and events like that. He had two very interesting findings:

1) One that we’ve known actually is people who are bereaved and who have lost their spouses, for example, in the week following the death, is a spike in the number of heart attacks. That’s a time to intervene.

2) Another very interesting finding is that people who have just had a cancer diagnosis, just a diagnosis, the pathology report, there is also a peak in heart attacks just at that time. Another good place to intervene. It’s important to intervene in these things at critical times.

DM: I couldn’t agree more. We really appreciate all the tremendous amount of information you’ve compiled through your careful analysis of this very large comprehensive trial, really advancing the forefront and really saving probably at least tens, probably hundreds of thousands, or millions of women’s lives by identifying that this was a serious risk factor and changing the standard of care in such a commonly prescribed practice, which is so difficult to do. Thank you for leading that effort.

SS: Well, thank you. We’re very proud of the accomplishment of all the participants and all the investigators. It’s a highlight of our professional lives, all of us.

DM: Yeah. Well, you’re certainly to be congratulated. That’s a major achievement. Any time you can save hundreds of thousands or millions of lives, that’s a good thing. Keep up your great work. We’re really so glad and delighted to have had the opportunity to connect with you today.

SS: Thank you. It’s a pleasure talking to you.

[END]