Hi. This is Herb Kressel and welcome to the May 2016 Radiology podcast. This month we have interviews with the authors of three very stimulating papers. First, I’ll be speaking with Dr. Matthew Davenport, Assistant Professor of Radiology at the University of Michigan who with his colleagues authored a study entitled “Indirect Costs and Harm Attributable to a 13-Hour Inpatient Corticosteroid Prophylaxis prior to Contrast-enhanced CT.” As you know these prophylactic corticosteroid treatments are widely employed and there have been questions about their overall value. I think readers will find this of interest. Next, I’ll be speaking with Professor Hildo Lamb of Leiden University in the Netherlands who with his colleagues in the Netherlands authored a study entitled “Association between Hepatic Triglyceride Content and Left Ventricular Diastolic Function in a Population-Based Cohort, the NEO Study.” This is a large population study looking at factors related to obesity and non-alcoholic fatty liver disease. I think this paper has some very provocative data and I think people will find this interesting clinically, scientifically, and on a more general level. Finally, Dr. Dave Kallmes, Deputy Editor of the journal for Neuroradiology will be speaking with Meike Vernooij Associate Professor of Radiology and Epidemiology at University Medical Center Rotterdam also in the Netherlands on her paper entitled “White Matter Degeneration with Aging: Longitudinal Diffusion MR Imaging Analysis.” We see a lot of cross sectional studies on changes and diffusion tensors and the like. This is kind of an interesting look at changes in diffusion over time and aging. Many of us boomers will no doubt find this topic of interest if not a bit depressing. We hope you enjoy this month’s podcast and as always welcome your feedback.

Indirect Cost and Harm Attributable to Oral 13-Hour Inpatient Corticosteroid Prophylaxis before Contrast-enhanced CT

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Matthew S. Davenport, MD Thanks for having me.

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ant clinical risk factors or comorbid diseases that might predict whether someone would be in the hospital longer or a shorter period of time. We found the rates of those were basically similar in all the different categories.

**H.Y.K.** So they were matched for some demographics but they were sort of fatty, reasonably equal distributions of relevant comorbidities that might affect length of stay.

**M.S.D.** That’s correct.

**H.Y.K.** You didn’t seem to consider allergic history, minor reactions, things that you might be interested in. How come?

**M.S.D.** Yeah the major reason for that is that at our hospital the policy is to prep for certain indications. So if somebody was to have that indication they would automatically be in the prepped group, and if they did not have the indication they’d automatically by default be in the non-prepped group so it would be impossible really to control for that.

**H.Y.K.** Now interestingly you also used a hypothetical cohort and what did you try to study with this group of hypothetical patients?

**M.S.D.** That’s right. So we had two different approaches to this. One was looking at the actual groups, what was their length of stay that may or may not be associated with the steroid prep; and then the other group was the hypothetical cohort where we said based on what we learned from our study cohort, can we try to model what the cost would be on a population level to try to prevent one reaction related death by using these steroid preps. So they’re sort of different goals, but same topic.

**H.Y.K.** How were the underlying assumptions that drove the hypothetical analysis determined?

**M.S.D.** So we conducted a sensitivity analysis for our hypothetical cohort and the purpose of that is to model the variability within a particular variable which we don’t necessarily know what the right answer is. Let’s say there’s a publication that came out and said the risk of death from anaphylaxis is X and another publication comes out and says well actually I think it’s Y, we can actually model that variation between those two estimates. So the way we did that was we looked at the published literature and the data from our cohorts to determine what the variable should be.

**H.Y.K.** Tell us what you actually found. What were the key findings in your study?

**M.S.D.** I was actually surprised at the signal that we found in the data. I was expecting to see a minor blip maybe, but it was a pretty strong signal. We basically found that inpatients who get a steroid prep, the 13-hour steroid prep, have a 25 hour median prolongation in the time from admission to CT, and they also have a 25 hour median prolongation in the time from admission to discharge. So they’re spending a day and some change additional in the hospital associated with the presence of a steroid prep. That was a big number to me. It’s interesting those numbers are actually identical that there was a 25 hour prolongation before the CT and the aggregate length of stay was 25 hours longer. Patients who got a prep actually tended to get discharged a little bit faster after the prep compared to people who didn’t get the prep after the CT and I think that’s because they were just tired of waiting around the hospital basically. And also we found that patients who got a steroid prep had a higher infection rate and we think the reason for that is that they had a longer length of stay. The infection rate per thousand hospital days was similar between the two groups so we don’t think it was enriched or sicker population, we think they were just in the hospital longer. The hypothetical cohort showed that, as you’ll see in figure 4, that to try and prevent a death from contrast in patients who have risk factors who’ve had a history of a prior contrast reaction, you end up putting a lot in the tank. You spend a ton of money, you indirectly are associated with a lot of hospital acquired infections and you indirectly are associated with a lot of hospital acquired infection related deaths. In the sensitivity analysis, even in the best case scenario where you model the most therapeutic benefit from a prep and the least harm from a prep, the model still shows you kill three times as many people as you save by prepping this inpatient vulnerable population. Those numbers were surprising to me, but at the same time maybe it’s not surprising.

**H.Y.K.** Just to make it clear, the relationship between the corticosteroid prep and the hospital acquired infection is really mediated by the length of stay. There’s no direct relationship between those two?

**M.S.D.** My hypothesis is that it has to do with the length of stay prolongation, but that’s a guess of course. I mean it may be that there’s some minor immunosuppression that occurs, but I think that’s less likely to be true.

**H.Y.K.** Okay. Now what about the outpatients? You sort of mention as a study limitation they didn’t really consider them. Can the results be extrapolated? A lot of this is length of stay related so presumably if you did it in your home you wouldn’t have that risk and then how might this actually affect policy? Would you contemplate changing policy for inpatient but not for outpatients?

**M.S.D.** Those are good questions. I think you cannot use any of the information that we have presented in this paper to make decisions about outpatients. They have a completely different set of risks, being at your home watching TV or taking a walk outside does not have the same risks as lying in a hospital bed next to your neighbor who has MRSA. So they’re just not really comparable populations. With regard to policy, that’s a tough one.
Hi. This is Herb Kressel, Editor of *Radiology* and today I’m joined by Dr. Hildo J. Lamb, Professor of Radiology at the University of Leiden, who with his colleagues from Leiden and elsewhere published a fascinating study on the association between hepatic triglyceride content and left ventricular function in a population-based cohort, the NEO study. NEO stand for the Netherlands Epidemiology of Obesity Study. Good day Dr. Lamb. How are you?

H.Y.K. Hello Professor Kressel. Nice to see you. Thank you.

H.Y.K. Good. Well the first question I’m sure on everyone’s mind is what is the Netherlands Epidemiology of Obesity Study? Tell us about it. How many people are in it and how do you get to enroll? Can I join?

H.J.L. That’s indeed an interesting question. The study is actually already finished so all the inclusions are completed. In total we had a complete study population of more than 6,600 patients and that includes people with normal weight that was the smallest group, and also people with overweight and with obesity. We defined this based on the WHO criteria. For us normal weight was a BMI of 25 or below. The overweight was between 25 and 30 kg/m², and obesity was more than 30 BMI. From all these thousands of patients we could not all put them in the MRI machine. It’s too costly and logistically really complicated. We had a sub group of 1200 patients entering the MR machine and because of technical reasons and of splitting in measuring the brain and the cardiovascular aspects in different patients, and we excluded also cardiovascular disease, liver disease and use of alcohol and statins; we ended up in the end with more than 700 patients who entered the database for this study.

H.Y.K. Okay good. Now just to go back, in the larger study what happened to those people once they were enrolled? Were they just monitored or did they have any intervention or what was measured?

H.J.L. It was set up as a cross-sectional study so they were all measured at one moment in time and the idea was to perform a real basic epidemiologic study and what we do now because it is already in follow-up for four to five years, is that we do a clinical follow-up. We have one measurement including all kinds of things, but also neurologic testing, blood samples, but also MRI of the brain, cardiovascular system, even of the knee in some sub groups; and the idea is to follow them up clinically. Check for events, check for new disease for treatment, sub groups; and the idea is to follow them up clinically. We have now made follow-up on those individuals and are currently analyzing the data.

H.Y.K. Okay. So let’s for your final pithy question let’s cut to the chase, Dr. Davenport if unfortunately you were a patient in a hospital and had a prior reaction, would you decline the corticosteroid prep based on what you know?

M.S.D. I’m going to give you a slightly nuanced answer. If my history as a prior contrast reaction, I’m getting the same class of contrast medium and my prior reaction was mild, I would decline the prep and say just go grab an epi pen and stand by, no prep. If I had a prior moderate or severe reaction, I might have a different thought about it. If my reaction was severe I would say please don’t give me contrast at all. I don’t want a prep or the contrast; and if my prior reaction was moderate, I’d consider getting a prep first.

H.Y.K. Okay, that’s fair enough. Very thoughtful. Great to speak with you again Dr. Davenport.

M.S.D. My pleasure.

H.Y.K. Thank you.
ship between non-alcoholic fatty liver disease and cardiovascular disease?

H.J.L. That’s actually one of the main topics we are researching now and also in other groups, research groups, there’s now a lot of interest that topic the relation between liver fat and cardiovascular function. Of course we don’t know exactly what the relation explains, but we have some ideas. Actually we think that the liver plays a center role in our lipid metabolism as already known in the past, but that the liver is also directing the delivery of fat to organs. We call that ectopic liver content. For example, in the vessel wall in the heart itself and in other organs like the kidney, there can be liver accumulation. And the idea is that...

H.Y.K. You mean liver or you mean lipid accumulation?

H.J.L. Yeah the lipid accumulation for example in the heart and the idea is that it leads to inflammatory processes to metabolic changes switched to for example lipid metabolism; and that all these factors combined leads to for example in the heart to reduce myocardia profusion increased stiffness of the muscle due to fibrosis or diffuse fibrosis, and now the link between the liver and the heart is that we think that we have first fat accumulation in the heart, then you have a sort of inflammatory process leading to diffuse fibrosis which leads to functional abnormalities.

H.Y.K. I see. Then in this particular study what specifically did you hope to learn?

H.J.L. Based on this idea of the diffuse fibrosis that we did not directly measure we wanted to find a sort of clinical outcome of that process and that is actually a diastolic function. A diastolic function also gets a lot more attention in the past few years because the interesting thing is that when you see subtle changes, clinical changes, in diastolic heart function then you can still reverse the damage. So that’s why we were interested in the relation between liver fat and diastolic heart function because when you can detect diastolic dysfunction in an early stage we can apply therapy to reverse the pathology.

H.Y.K. How did you, I guess you alluded to this a little bit, but how did you actually determine the sample size for this study and did you think it was well powered when you began?

H.J.L. Actually when we started we were aiming at the overweight and obese categories so it actually was determined as a BMI of 27 kg/m² and higher to include, but when the study proceeded we also like to include sort of normal weight group and that group was a little bit underpowered because it was added on later and we had a sort of standard time frame for the study to be completed, but the total sample size of the overweight patients was actually based on blood measurements and all the other measurements we do like the neurologic testing and all the clinical stages. That’s why we ended up with a couple of thousand studies in the total study and based on our experience with standard deviations on the MRI measurements we could decide to lower the number of MRI examinations to a more reasonable number to scan in a few years.

H.Y.K. I see. What specifically did you do in your study and what did you find?

H.J.L. What we did and that is nicely depicted actually in Figure 2 is that we measured the fat of the liver using MR spectroscopy. That was a single volume measurement at a sort of standardized location in the liver. What we did there is that we acquired just a water spectrum without suppressions and then you measured water content of the liver in that certain area, and after that we applied the same acquisition but then with water suppression and with that technique you actually zoom in to the fat signal and if you then divide the fat signal by the water signal you get a relative fat percentage of the liver in that area. What you see in the figure 2 is that on the left side on the top you see a typical spectrum of a normal weight volunteer; you see very high water and very low fat signal that is the back row. When this is quantified in this example the fat content was about 1.5% so that is completely normal. We consider a fat percentage below 5.5% as normal. And then in the middle you see a patient with overweight. They still have a normal fat percentage in the liver, but it’s higher. It’s now about 3.5% fat. On the top row on the right you a patient with obesity and there we see a fat percentage of 7% so that is really a fatty liver. The other measurement was based on flow imaging with MRI. Flow imaging across the mitral valve in the heart and there you can measure the way the heart fills. Actually how the heart fills is in an early wave this sort of passive filling because you have a pressure gradient between the left atrium and the left ventricle so the blood enters the left ventricle passively. That’s the early filling wave. The second filling wave that’s caused by atrial contraction. So that’s an active process. We know that in a lot of diseases you have a compensatory mechanism that when the heart becomes stiffer because of fibrosis for example, may be based on fat and inflammation in that respect, then you have a change. Then the early filling goes down because the heart is stiffer so it cannot relax fully. The heart enters not so well, but then the atrial contraction becomes more important. What we calculate is the E/A ratio, the ratio between the early and the atrial filling. Then on the bottom row in Figure 2, you can see that in the normal weight volunteers you see that the E wave is higher than the A wave. It is actually quantified as 1.3 as the E/A ratio. But then on the other end of the spectrum on the right in the obese patients, we see an E/A ratio of about 1.1. So then the E wave is almost similar as the A wave. It shows that the heart is compensating for the what we think is the difference in compliance the elasticity of the left ventricle changes. That is actually accompanied also by an increase in fat content in the liver.
H.Y.K. Okay. If I understood this correctly, you found that the hepatic triglyceride content was associated with diastolic function independent of other confounding factors included the metabolic syndrome in the obese individuals, but not necessarily in the other weight groups. What is the likely explanation for this?

H.J.L. We think that this is mainly related to a power problem. That relates to the design of the study because we started an inclusion of BMI 27 or higher and actually there was most emphasis. So actually we cannot say anything about the overweight and the normal weight group. We need more subjects.

H.Y.K. Okay so it’s almost like you have a part A and a part B of your study. The part B is the obesity and that’s better powered and the relationship is clear. It occurred to me you used MR spectroscopy which is a very recognized reference standard, could you have used ideal or one of the imaging tests that developed the fat fraction would that have been as useful or do you need to look at the specific fat types?

H.J.L. That’s really an interesting question. Why we used spectroscopy in this study is more historical reason because we started doing this while the idea originated in 2006 and actually started scanning in 2008; and at that time the for example Dixon techniques were not so developed yet. We were also trying to validate the technique at that time, but for future studies indeed these fat fraction imaging techniques are very interesting because what we measured now is just one small location in the liver, but actually we cannot tell anything about heterogeneity of the fat distribution in the liver. That’s indeed very interesting for future work.

H.Y.K. And I also note that you had a failure rate in the MR spectroscopy of around 10% which seems, well certainly if you’re doing sort of the Dixon type techniques it should be much, much lower than that. What were some of the problems in collecting the spectroscopy data?

H.J.L. That’s mainly related to the setup of the study. We scanned those patients in a 1.5 T-mobile MRI scanner that was hired for the study. It was scanned by regular MR technicians. In the beginning we were training them for the functional imaging and all the standard imaging for the brain and the knee and the heart and the vessels and spectroscopy is quite hard for them to learn. So actually the 10% problems were in the beginning of the study.

H.Y.K. I see, learning curve issues.

H.J.L. Yes.

H.Y.K. Okay now in the discussion of your paper you note the results of other groups and actually your results are somewhat discrepant to a number of studies that you referenced done in Asia. Do you think this is again a sampling size issue or might there be other differences in the Asian population that might account for some of the differences?

H.J.L. Yeah I think this is also a very interesting point. Of course we have the sampling issue between all the different studies, but actually we are also performing now other studies in other sub-groups. For example we are now working on a study in Hindustani and the first results show that indeed they have different type of fat distribution throughout the body so maybe there can also be difference in different population. Also for example as shown in the MESA study they observe different normal values for even simple measures like ejection fraction in diastolic volumes. This is also very interesting to compare different populations and define normal values for specific groups of patients.

H.Y.K. Right. Well this seems like an incredibly important and fascinating research area. For your group it sounds like the NEO study is sort of closed up. What do you think are the important next steps for research in this area?

H.J.L. What we will try to do but that’s a challenge to finance the whole program, but actually we are not setting up NEO 2.0 study. What we would like to do there is based on these measurements. We would like to do all measurements in all patients now. In the meantime we had a lot of technical advancements for example the new fat fraction imaging techniques which speed up the acquisition. Also we can now do total body fat distribution measurements. We can also do many other things to measure in the liver and heart function; diffuse fibrosis and all the newer techniques. What we try to do now is perform all these scans of the heart and the whole cardiovascular system in a new batch. The interesting thing is that of course we then have a follow-up of the patients who are already in the 1.0 NEO study.

H.Y.K. Okay. Well this is really interesting stuff. Thank you for your paper and for joining us in a discussion today. It’s been a pleasure.

H.J.L. Okay. Thank you very much for the opportunity to explain the details.


David F. Kallmes, MD  Hello my name is David Kallmes. I'm Deputy Editor for neuroradiology. Today I'm joined by Meike Vernooij who is Associate Professor of Radiology and Epidemiology at Erasmus Medical Center in Rotterdam. She is here to talk about her paper “White Matter Degeneration with Aging: Longitudinal Diffusion MR Imaging Analysis.” Welcome Dr. Vernooij.

Meike W. Vernooij, MD, PhD  Thank you Dr. Kallmes. Thanks for the invitation and to talk about our paper.

D.F.K.  Sure and before you start give us just a thumbnail sketch of the Rotterdam study.

M.W.V  Sure. Well the setting in which we conducted this study is indeed in the setting of the Rotterdam study which is a large population based cohort study among middle aged and elderly participants. They are all originate from the same suburb in the town of Rotterdam. The entire Rotterdam study consists of close to 15,000 people and it has been running since 1990 and the main aim of the study is to study causes and consequences of age related diseases and among those neurological diseases are one of the main topics that we’re studying and then mainly the neurological diseases that are very frequent occurring in older age such as stroke and dementia. What we do in the Rotterdam study is we follow people, we invite them to our research center, we do an entire check up with interviews, medical examination, and then we follow them every three to four years for change in a set of biomarkers that we assess and we also continue to follow them for occurrence of major events. In 2005 we incorporated in the core of the study particle brain imaging. We have a dedicated research scanner with indicated research technologies. We scan every participant who comes to the research center. Right now we have over 5,000 unique baseline scans in our participants and up to 3,500 people have had longitudinal imaging and our imaging protocol consists of structural scanning and a bit of functional scanning. It also includes resting state fMRI and for structural scanning we do T1 weighted imaging, T2 weighted and FLAIR imaging to look at brain tissue volumes and white matter lesion volumes. But we also have a diffusion-tensor imaging sequence in the protocol to study microstructural change in white matter. That is what the current paper mainly focuses on. The specific aim of the current paper was to study longitudinal changes in diffusion properties of the white matter over a two year time period. We did this in a set of participants in a Rotterdam study and whom we had longitudinal data and longitudinal DTI data at that point which is in now over 500 participants with a mean age of close to 70 years. I think the age range was 64 to 91 years. We mainly studied fractional anisotropy so the degree of directionality of diffusion along white matter tracts and mean diffusivity which is mainly the degree of displacement of the (inaudible) molecules perpendicular to the tract.

D.F.K.  What were your major findings from these 500 longitudinal studies?

M.W.V  We assessed these diffusion property changes both globally so over the entire white matter and voxelwise and I think our main result is that when we looked at these changes over two-years’ time we saw that widespread in the white matter we saw that both FA decreased and MD increased. Both of which reflects a worse microstructural integrity of the white matter which is something that we could expect but that was all based on cross-sectional studies because up to now the main work of other studies in using diffusion-tensor imaging has been done cross-sectional also in aging in which we saw that with increase in age the white matter structural integrity decreases. But this was hardly shown in longitudinal setting which is very important because in the cross-sectional setting we only look at accumulated change and we want to see how in a short time period these changes occur and whether you could really capture them and potentially use those in a clinical setting and to understand to be able to monitor white matter changes over time. So we see that even over relatively short time period we see that they’re widespread changes which I can show if your look at Figure 2 in the manuscript. This is actually showing us the main finding with change in FA and MD over time. In the top row we see how FA changes over time and the red color indicates regions where FA decreases over the two-year time period. In the bottom row we see mean diffusivity MD change over time and the blue color indicates the increase in MD. As we can see, this is projected on the white matter skeleton as used in tract based patient statistics. That’s the method that people working with DCA/DTI data are very familiar with. This essentially shows the core of the white matter skeleton and the center of the tracts and as we can see very widespread of the center of these tracts are changes in FA and MD. What we should note here is that these are changes in normal appearing white matter. So this was not white matter that appeared completely normal baseline. So we excluded all the white matter lesion voxels that were present at baseline. What is furthermore noticeable is that it is important to stress is that these changes were apparent and were significant even after we adjusted for the amount of white matter atrophy and white matter lesion volume that people had. So these would be often called microstructural markers of white matter disease. And when we adjusted for these we still found these microstructural changes. So that means that...
above and beyond these microstructural changes you can really measure these microstructural changes over time. One other thing that I would like to note in Figure 2 is that even the – so the red color shows the decrease in FA so that’s the direction that you would expect and a decrease in integrity in the white matter, but we see some small blue areas in the top row and that indicates that there is an increase in FA over time in these areas which seems very paradoxical because we would expect of course that there’s only a deterioration in white matter over time. But it is less paradoxical if we realized how FA is measured and FA indicates a directionality of water diffusion in voxels, but of course we know that white matter tracts in the brain can cross and there’s actually many, many crossing tracts in the brain. If in the voxel in particular a voxel two tracts cross within that voxel and only one of the tracts, so then in that voxel the entire FA for that voxel is averaged over those two tracts, but if only one of these tracts deteriorates over time and the other tract is reserved, we can measure sort of paradoxical increase in FA because that one tract that is reserved has a much stronger directionality suddenly than the average of the two tracts in the voxel. And that probably what we see happening here because if we look at those blue voxels in the top row, we see that they are mainly present in the area where we expect the cortical spinal tract and the motor fibers to work through. We see very neatly in the centrum semiovale in the internal capsule and of course we can understand that one of the tracts probably is preserved quite late in life is the cortical spinal tract. So probably the paradoxical increase in FA that we see here is resulting from this crossing fiber phenomenon and the preservation of the cortical spinal tract which is supported by the fact that in this cortical spinal tract we do see an increase in MD as we see in the bottom row so we do see that the entire diffusivity increases but it’s just the directionality that becomes a bit more stronger in one direction compared to another direction.

D.F.K. Were you able to correlate this with patients’ age? Do you have enough of spread in age to look at the impact of age on the temporal findings?

M.W.V Yes. Another finding that we did on top of this is if we looked at patients’ age we saw that there was no linear effect of age on the loss of microstructure integrity in the white matter, and we saw that particularly people at old age had steeper declining white matter integrity which may be not of a big surprise but it hasn’t been shown before because this was something that we could not study in cross sectional designs and it is important because it could indicate or it indicates that up to high age the white matter loss is probably more pronounced at younger age and making it a very important time window to still try to preserve this white matter.

D.F.K. So the change is accelerating over time?

M.W.V Yes they are accelerating over time so there’s affect modification by age.

D.F.K. And you also looked at potential risk factors such as cardiovascular risk factors and the impact on the microstructure?

M.W.V Yes indeed. We looked at several cardiovascular risk factors among which blood pressure, diabetes, smoking, cholesterol level and we also included BMI and we also included APOE genotype being most important risk factor for dementia and surprisingly we found hardly any associations between these risk factors and the loss of microstructure integrity which might be explained by a couple of factors. One might be that the timing of a full two years might be relatively short to really find these changes so we might have been a bit underpowered. Another potential explanation is as I’ve shown in Figure 2 that we mainly looked at tract centers and we use this white matter skeleton and it might be that tract centers are less affected by cardiovascular factors and the changes might occur more in the tract periphery. But I think the most important explanation actually is that we know of course from previous studies the cardiovascular risk factors have an effect on white matter. We know that all these risk factors that I just mentioned lead to white matter atrophy, lead to white matter lesions, so it is surprising that we don’t find something with white matter structural integrity, but the most important explanation probably is that all of those cross-sectional results look at accumulated change over the life span and then look at one time point and then find for example if hypertension relates to white matter lesion volume whereas we didn’t look at disassociation with the baseline, but we only looked at the change over time over a very short period and potentially these changes are just smaller in relation to the whole accumulated change up to that point.

D.F.K. And you say you also did APOE risk factors as well, what did you find there in terms of cognition and white matter microstructure?

M.W.V With APOE we also had a surprising result. We found no loss of microstructural integrity over time at first with the APOE-ε4 genotype, but we paradoxically found actually some regions where they seem to have a decrease in mean diffusivity meaning less loss of microstructure integrity versus non-carriers. But when we looked at this more closely, we found that when we looked at the baseline results and the baseline DCI measures in APOE-ε4 carriers versus non-carriers, we found that APOE-ε4 carriers actually had higher MD and lower FA so worse microstructural integrity compared to non-carriers, so even though they seemed to be doing a bit better over a two-year time follow-up, their start was worse. That might indicate that their brain damage caused by the APOE-ε4 genotype probably had already occurred before we started to follow them up. So that might mean that that damage already occurs earlier in life so that later in life if they have seemingly less damage compared to the non-carriers which might also relate a bit to a healthy selection or a healthy survivor bias that perhaps the persons with APOE-ε4 genotype in our study
being a population based study, might have been a bit healthier relatively compared to the non-carriers.

D.F.K. Did you correlate any clinical or neuropsychological outcomes with the imaging findings?

M.W.V Not in the present study but as in the entire Rotterdam study one of our outcome measures is cognitive function and cognitive change. We also have done in the past and we are currently performing studies looking at relation between DTI measures and cognitive function. We found in the past when we looked globally for the entire white matter, we found that FA, MD and the entire white matter relates to cognitive function with people with lower FA and higher MD having the worst cognitive function and again this is on top of and beyond the presence of white matter atrophy and white matter lesions. What we are currently also doing is looking at specific white matter tracts to see whether, because the white matter of course is not an entire (inaudible) substance but is actually divided into functional different tracts and how these relate to cognitive functioning and we see again quite similar to what we’ve shown in the present manuscript that there’s a widespread loss of white matter structure that relates to cognitive functioning, so there’s many tracts to contribute to cognitive decline over age. I think if we think about how we can use the results for the present paper and translate them more to clinical setting for example, what we show in the present paper is particularly a magnitude of the microstructural changes in the white matter over time, that these can be the basis to for example define what is normal because it’s very hard. We understand that to a certain extent for example with a normal volume of the hippocampus is and we use that measure the biomarker in clinical practice, but for a new measure like microstructural integrity we are in need of reference values and often understanding of what is normal in order to be able to translate that to an individual person and decide whether his or her change over time or an acceleration of white matter microstructural damage is in line with what we expect adjusted for age and sex or whether it’s more pronounced.

D.F.K. Thank you for your time today and congratulations on a fantastic paper. We look forward to more papers from your excellent group going forward.

M.W.V Thank you very much.