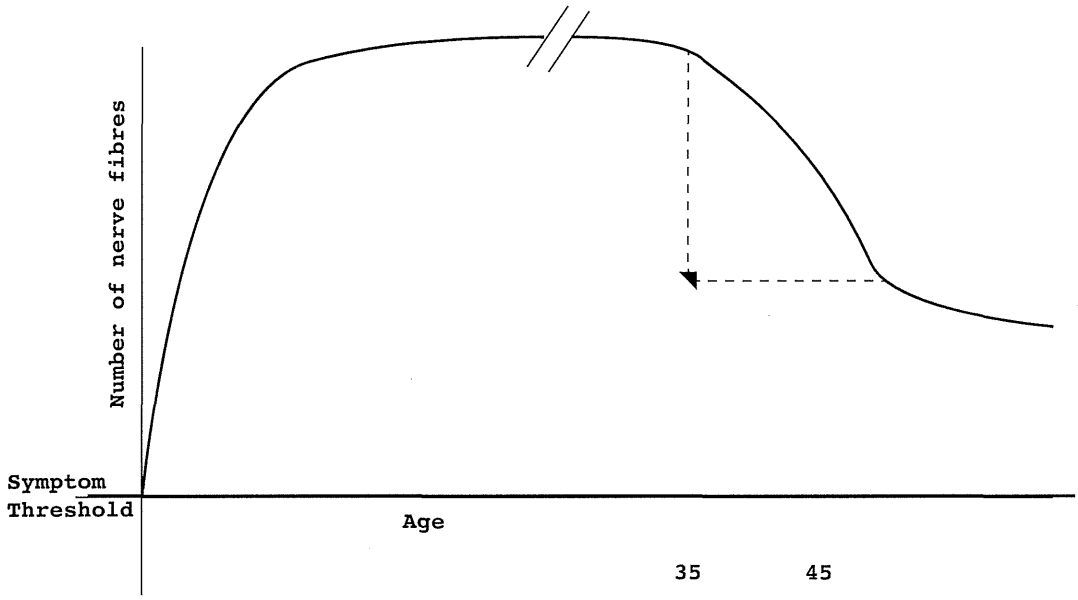
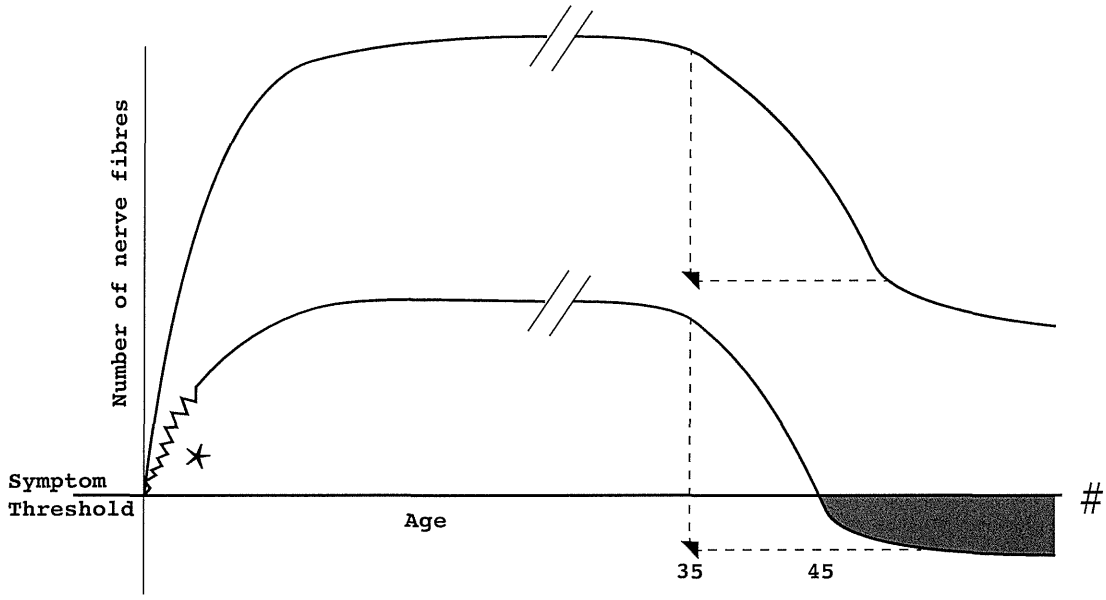
**Normal aging causes loss of axons but no symptoms**




or intrusion of a neurotoxin). Second, at middle age comes an additional loss of axons, a physiological process common to all peripheral nerves. In previously damaged nerves, the second bout of axon reduction cannot be absorbed. Surplus axons are all used up and the symptom threshold is breached. Symptoms of neuropathy erupt.

**Previous damage ✳ to peripheral nerves, plus age changes, results in neuropathy in middle age #**



## Conclusion:

Neural crest injury explains all features of thalidomide teratogenesis. Consistent quantitative neuropathology has been found in adults, children and animals damaged by thalidomide. Conversely, no bone, cartilage or other histopathology was found to indicate primary skeletal disease. Disordered skeletal architecture in the absence of skeletal histopathology is consistent with primary nerve damage causing secondary skeletal growth disorder.

Skeletal morphogenesis emerges as a 2-stage process:

- an initial undifferentiated stage of high nerve-dependency associated with neurotrophism, and
- a second stage of differentiation with reduced nerve-depen dency.

Thalidomide acts in the nerve-dependant stage before differentiation, ie. in the first stage, not the second stage of morphogenesis. Thalidomide poisons neural crest/sensory nerves during their early embryogenesis, disabling all nerve functions, including neurotrophism. This halts mitoses, which reduces the mass of undifferentiated mesenchyme within bands of segmental nerve supply.

Thereafter the second stage proceeds. The rest of the limb differentiates, minus the damaged neural segment/s. The size, shape and architecture of
the limb is altered, but not the skeletal cells.

Neural crest defects comprise a large collection of various disparate birth defects, adjacent to the well-recognised group of neural tube defects.

Within the large lexicon of medical diseases, thalidomide embryopathy belongs within the group of sensory and autonomic peripheral neuropathies. To suggest that thalidomide does not attack the neural crest is seen as absurd by informed neurologists, pathologists, paediatricians, radiologists and other medical practitioners who realise that neural crest injury explains the embryopathy.

The neural crest theory will not go away. It has a life of its own because it explains observed facts.

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**Hinoshita**： Thank you very much, Dr. McCredie. As she said she suffered from a little bronchitis. Because of her problem she decided to present this presentation using the video. She focused on pathology, radiology and pathogenesis of thalidomide embryopathy. By the way, do you have any questions? If you have, please raise your hands. Yes, Dr. Morrison, please.

**Morrison**： Hi, I'm Dr. Morrison, Medical Advisor to the Thalidomide Trust. I just wanted to say we are all entitled to have different opinions. However, in 2014 the World Health Organization held a convention in Geneva for medical experts to try to reach a consensus regarding the causation and diagnostic criteria for thalidomide embryopathy. With regard to causation there was most interest in the work around cereblon. This was the theory the experts chose to take forward. In addition regarding the classification of damage the medical experts proposed to support an algorithm. Hence The Thalidomide Trust currently supports the work of cereblon going forwards as causation of the embryopathy not the neural crest origin. The Trust also, when we look at new claims, understand that upper limb damage is bilateral, although there can be differences between the limbs. The medical experts at the WHO conference in Geneva discussed this aspect and agreed that if one upper limb was affected that the other limb would also be damaged. And lastly, just looking again we have an eminent neuro-orthopedic doctor working with the Trust. He is examining many affected by thalidomide embryopathy and he very much states that he can find nothing to support the view of the neural crest origin causing the problems from thalidomide. He felt it should be obvious when he examines them and though he has looked he cannot find any evidence that the neural crest is the causation. So, though I appreciate we all can have different opinions, at present this is the belief at the moment within

Thalidomide Trust.

**McCredie：** Well, I agree with you that there's plenty of room for other opinions. But I'm disappointed that the Thalidomide Trust is going to open a (####@01:49:32) because I think it's going to be a waste of time.

**Morrison：** OK.

**McCredie：** I must say most of the work I've done has been done with the Department of Neurology in Sydney University, which at that stage was heavily geared up to examine peripheral neuropathies that had all the laboratory tests and so ready to run on peripheral neuropathies. And that team entirely believed what they were saying. So, two different opinions.

**Hinoshita：** Uh-huh. It seems she has made much of the malfunction for the injury of the neural crest. And recently, the mechanisms of thalidomide have been researched in detail, and the drug also influence the new angiogenesis in our bodies. So, is there anyone who'd like to give some comment on the pathogenesis of thalidomide embryopathy? How about Professor Kayamori?

**Kayamori：** It is popular to believe that pathogenesis of the thalidomide embryopathy might be angiogenesis prevented from new formation by thalidomide. Thus, they are trying to treat cancer by using thalidomide medicine at present.

**McCredie：** If in the timelines that I've showed you with Lenz's sensitive period, the formation, or the first emergence of the limb bud according to Professor Nishimura, day 28, is that four-day period when there is no limb bud and they are no limb blood vessels, but there is the nervous system setting up already from the neuraxis. So that's a problem with the people who want to postulate acting on blood vessels-the fact that there are no blood vessels to act on, but the nerves are there to act on. That's number 1. Number 2, I think that the oncologist desperate of course to get new kinds of treatment, you can see the attraction when they read this angiogenic hypothesis to try that in cancer patients. What they actually did if you read the neurology report after they began doing that, the neurologists were very agitated because they were creating another epidemic of thalidomide polyneuropathy. And the third thing I'd say is that even going back to the original German epidemic of neuropathy when they used to do them out as a sedative, it produced neuropathy, it didn't produce anything angiopathtic, there was never any angiopathology shown. So I don't know what...Why they're trying to do that is because they can see that thalidomide can stop cell division. But, they're not taking into account what killed the sensory nervous system to stop the cell division.

**Kayamori：** I want to ask about one thing. You mentioned about no sparing of central nervous system. Could you give us knowledge of peripheral nerve involvement? For the first time of thalidomide scandals, they reported lots of involvements of peripheral neuropathy axonal type. But we didn't get such evidence in Japan. And from a point of electrophysiology just examining patient whether patient is involved in peripheral neuropathy or not, I couldn't find generalized neuropathy except for entrapped neuropathy. So we considered there was no pathology in the nervous system, in the peripheral as well as the central nervous system.

**McCredie：** Probably the bi-polar neuron has two arms. And alone that diagram I showed you wither

in the back, from the distal end. There's also some withering in the central end going up to the central nervous system. And MRI I think that spinal cord has shown depletion in volume of the posterior colons going up to the brain. And so, undoubtedly in the brain, there are going to be a fix. But they weren't reported at first of course in the babies, but I think they are, some affects they talk about autism, perhaps an increase in the incidence of epilepsy, these things creep in and out of the literature. There is obviously going to be some affect up there on the other end of the bi-polar neuron.

**Kayamori**: Someday, if you will come to us again, I have a discussion, I would like to discuss more and more. Thank you.

**McCredie**: OK. I have two graphs to show you then too.

**Hinoshita**: Is there any comment or opinion from German researcher or physician? Professor Peters, do you have any comment or opinion about the pathogenesis of thalidomide embryopathy?

**Peters**: No electric involvement as well as no angiogenetic involvement. Maybe it's both. Depends, difficult.

**Hinoshita**: Is there any other question about her presentation? Then, thank you very much, Dr. McCredie. OK now it's a little behind the schedule, but we will start our lunch time and poster session. When it comes to the poster session, the discussion will be done during the time from 12:15 to 13:10, OK? Please stand by the posters for the poster presenters. Anyway, until 13:10, I would like to have lunchtime. Thank you very much for the former part.

**Staff**: This is an announcement for the restaurant information for the Japanese language speakers. Actually there are many coffee shops and restaurants available in the ground or basement floors of this building. So, please do join us once again for the afternoon part, which will be starting at 1:10 PM. And also meanwhile there was an English announcement already and actually there is the post presentations, and Q & A will be particularly held from 12:50 to 1:10. There will be a 20 minutes long for Q & A session. So if you have any questions or have some discussions with the presenters, please do join us in the poster presentation area during that wind of the time. Thank you for your participation.

**(Lunchtime)**

**Staff**: You'd like to resume the afternoon session. Dr. Hinoshita, please start.

**Hinoshita**: You could take enough rest and have a productive discussion with the poster presentations. Let's start the afternoon part of this symposium.

### ④Dr. Christina Ding-Greiner

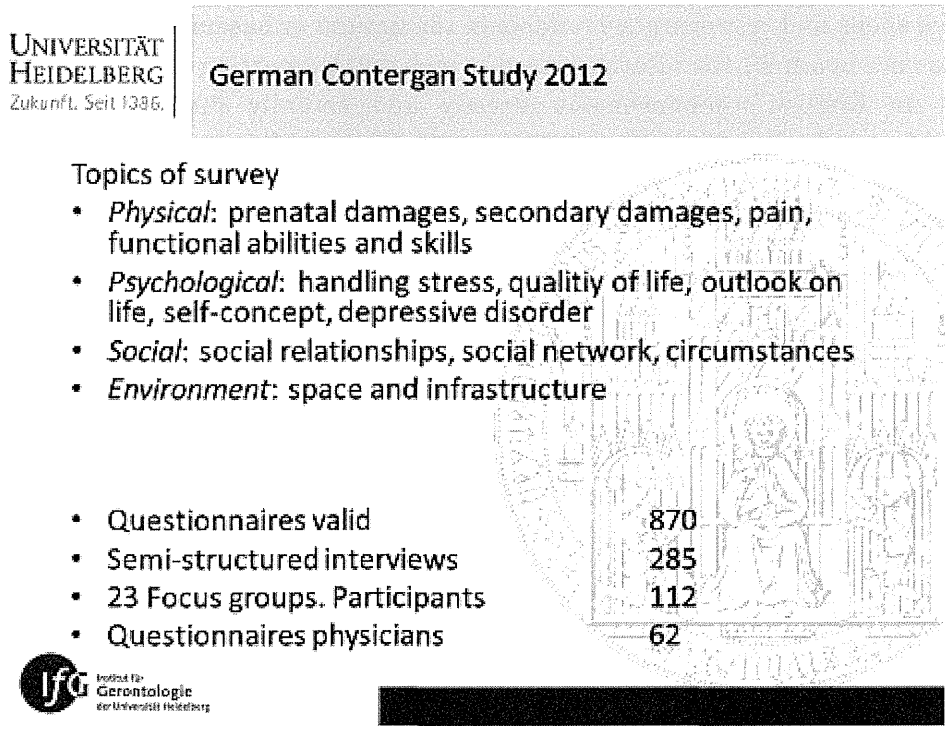
### "Aging with Thalidomide damage.　The German survey. "

First of all, the oral presentation will be given by Dr. Christina Ding-Greiner. Ageing with Thalidomide damage -- German Contergan Study 2012 and Evaluation 2015. I will introduce her briefly. She got the thesis and M.D. at University of Heidelberg in 1970. She stayed in San Francisco, California around

1980 for three years. She has been working at Institute of Gerontology, University of Heidelberg. She has main topics in research in some different projects. First, physiology of ageing, stroke prevention, and rehabilitation. Ageing of mentally disabled people and patients with psychiatric illness and interaction with nurses and caregivers. Development of concept of good care. Healthcare and prevention in elderly women. Preservation of motivation and productivity in elderly employees ageing of victims of thalidomide.

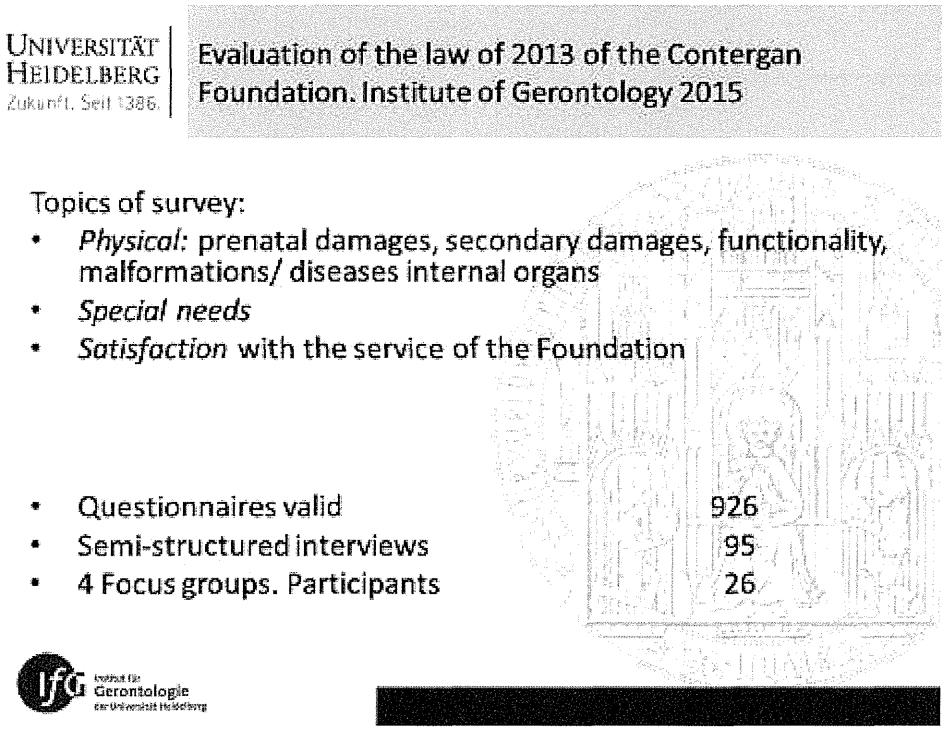
Anyway, she has so many research topics. Then Dr. Ding-Greiner, please.

**Ding-Greiner：** Thank you very much for your invitation. I'm very happy to be here in this beautiful city and to be allowed to speak to you.
The two studies Dr. Hinoshita mentioned give us an overview of the current living situation of victims ot Thalidomide and of future health care requirements. The aim was to identify existing care deficiencies and special needs to be able to give them better care and support. Based on our results, I want to emphasize the health situation of our participants, because this is of increasing importance for the years to come, not only for Thalidomide affected people, but for all people who have to deal with health problems of victims of thalidomide.
Thalidomide affected people are quite different from other groups of impaired people, even from those, who have apparently similar malformations, because they suffered a prenatal intoxication with Thalidomide. Therefore they are a very heterogeneous group concerning their damages. The Institute of Gerontology in Heidelberg is a theoretical institute, we have no opportunity to do clinical research or even to do some diagnostics. We get all our results by questioning our participants, and our participants are the experts on Thalidomide. Our results are based on the statements of a total of 1,267 participants in two surveys, the German Contergan Study 2012 and the Evaluation 2015.



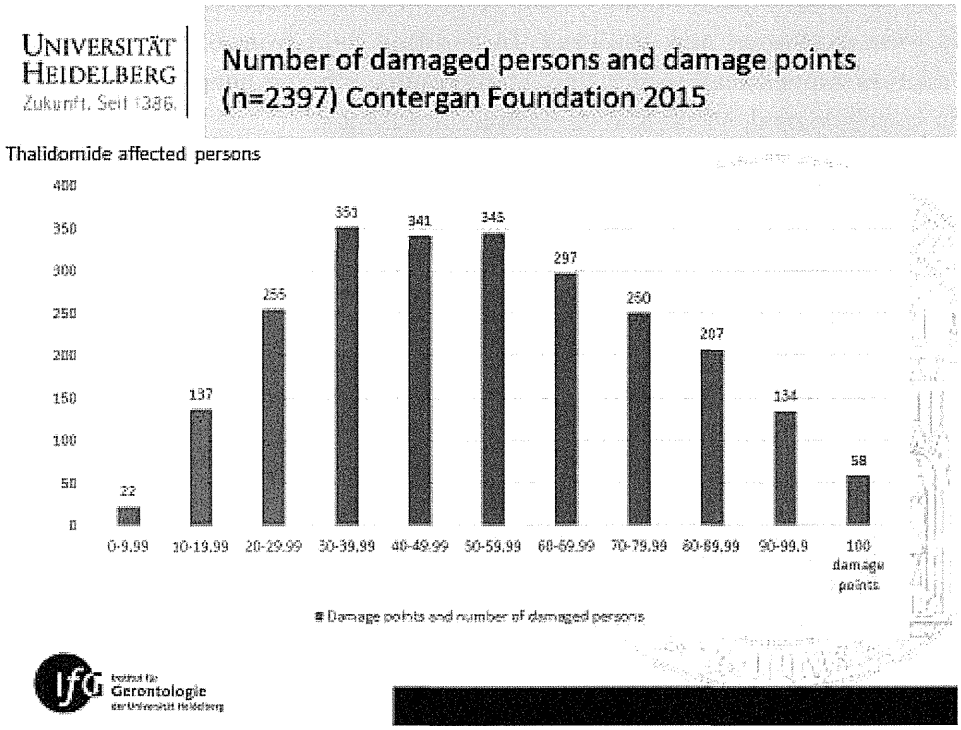
In the German Contergan Study (2012) 870 questionnaires, 285 semi-structured interviews and 23 focus groups with 112 participants were evaluated and analyzed. In addition data from 62 questionnaires were collected from medical doctors experienced in treating Thalidomide affected people. The topics of the survey dealt with somatic, psychological, social and environmental issues.

As a consequence of the results of the survey of 2012, the living situation of Thalidomide impaired people changed by modification of the Law on the Contergan Foundation for Disabled People as revised by the Third Amendments Act 2013. The financial compensations were considerably increased and in addition financial means of 30 million EUR were provided for special needs.
In 2015 the Institute of Gerontology had the opportunity of realizing an evaluation of the effects on the living situation of Thalidomide affected people induced by the new law. Questionnaires were developed. The evaluation included 926 valid questionnaires, 95 semi-structured interviews as well as 4 focus groups.



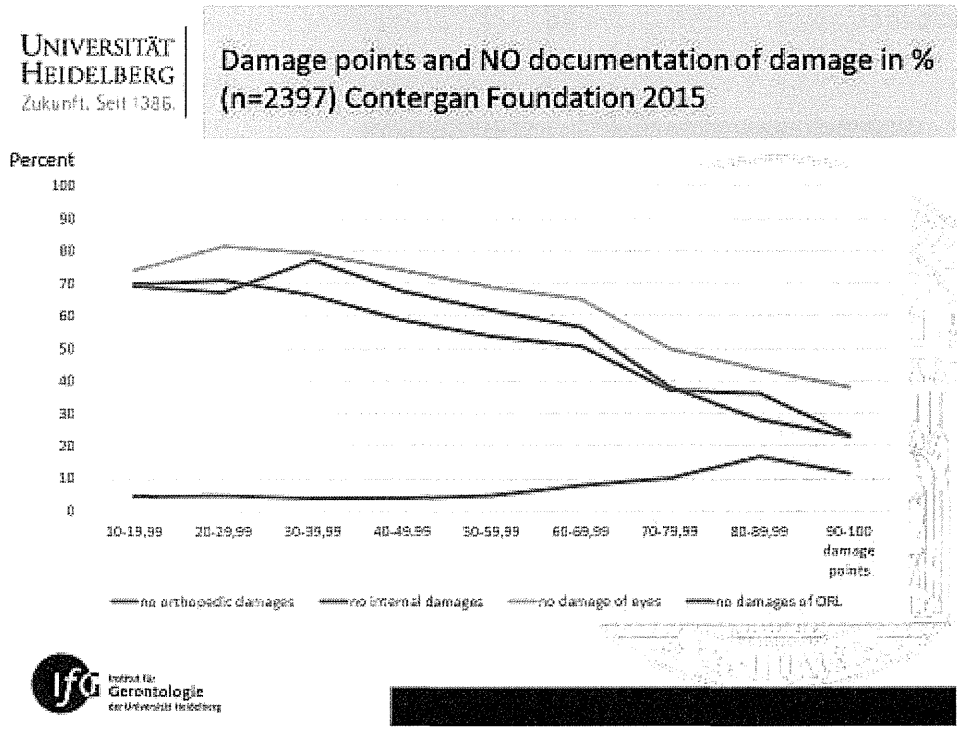

The topics of the survey were issues concerning somatic problems, special needs and satisfaction with the services of the foundation.

The foundation has its own system of evaluation of the prenatal Thalidomide damage in different organ systems. People get damage points e.g. for orthopedic damage, for damage in the eyes, in the ears, and in internal organs. Only verified prenatal damage is evaluated and gets points. The more damage there is, the more points people get up to a maximum of 100 points. The amount of damage points is decisive for the amount of the financial compensation.

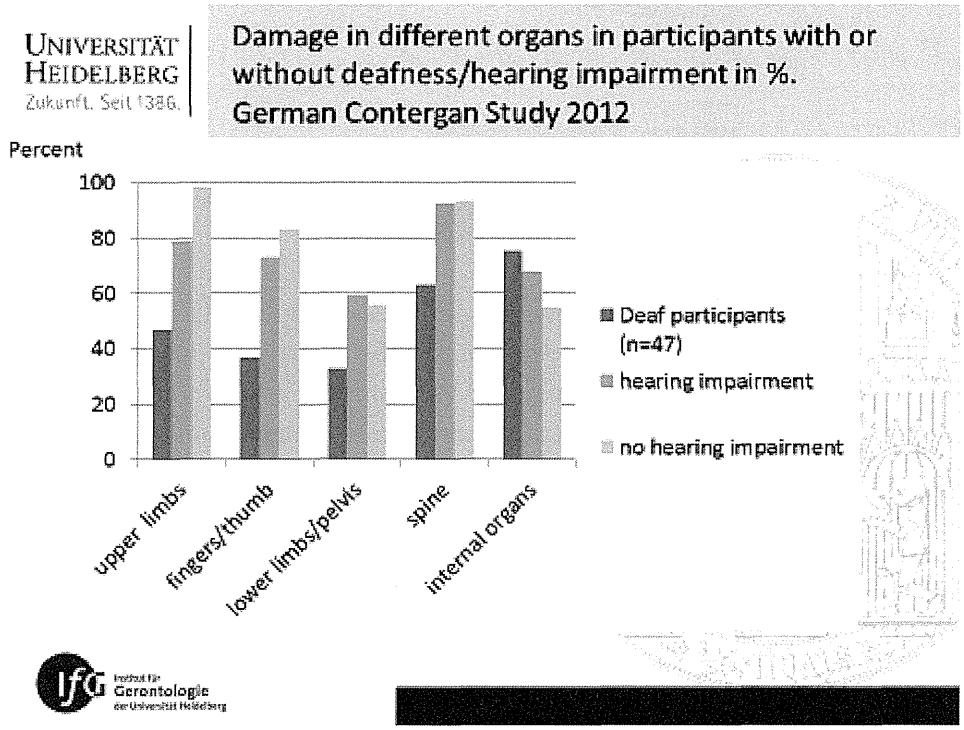



More or less half of the population of Thalidomide victims in Germany have an average of 30 to 60 damage points. Thalidomide impaired people with less than 10 points get no financial support. Today they are mostly in trouble, as they led a life as normal as possible, and up to now they developed severe secondary damages caused by physical overstrain.

The Institute was provided by the foundation with data about the recorded prenatal damages in different organs and the amount of affected people, respectively.

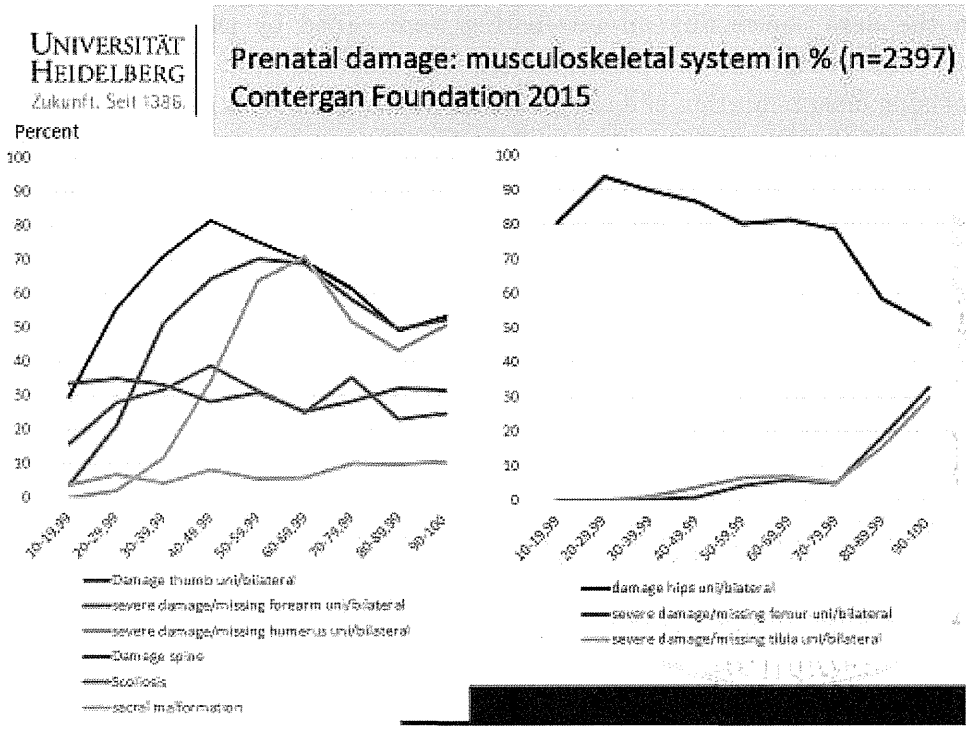


In this figure can be seen the data concerning an interesting item called by the foundation 'no documentation of damage'. As can be expected the thalidomiders with a low amount of damage points have a high percentage of missing documentation of damage in internal organs, eyes and ear, nose and throat medicine. The percentage diminishes in the groups with an increasing amount of damage points. The only exception are the orthopedic damages. Not documented orthopedic damages tend to increase the more points affected people show which means that the amount of orthopedic damages decreases in a population of thalidomiders with a high amount of points. An explanation can probably be found in the comparatively high amount of Thalidomide affected deaf people. 82 deaf people participated in the evaluation 2015 and 42 in the survey 2012. There are about 212 persons who suffer from hearing loss admitted by the foundation. In comparison to thalidomiders without hearing loss the deaf population shows a smaller amount orthopedic damages.



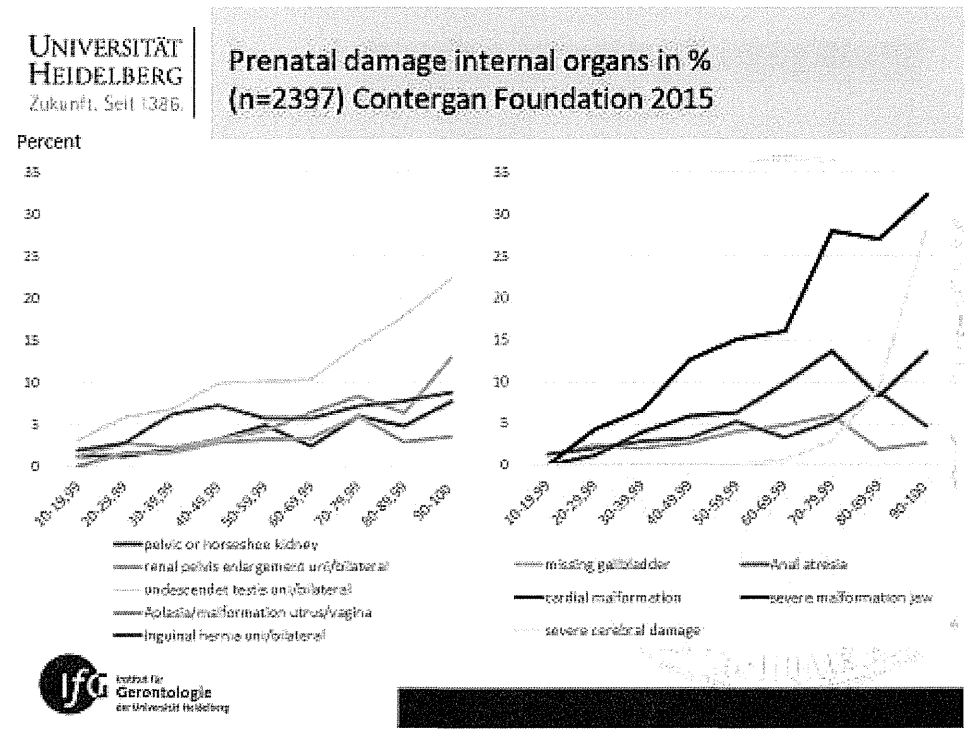

This figure shows the data of the German Contergan Study 2012. Participants with hearing loss show about half as much orthopedic damages than the group of participants with hearing impairment or without any hearing impairment. In deaf participants the spine is affected more often than the upper and lower extremities, damage of the internal organs is more frequent in this group than in the other two groups. Participants with hearing loss suffer from muscular weakness, too. They complain of severe problems when working physically, they start shaking and they need an increasing interval to recuperate, they show a high tension of the muscles. Deaf thalidomiders may be impaired in mobility in spite of missing orthopedic damages.

The following diagrams describe the incidence of different damages in percent in relation to damage points in the whole population of Thalidomide affected people. Data were provided by the Foundation.



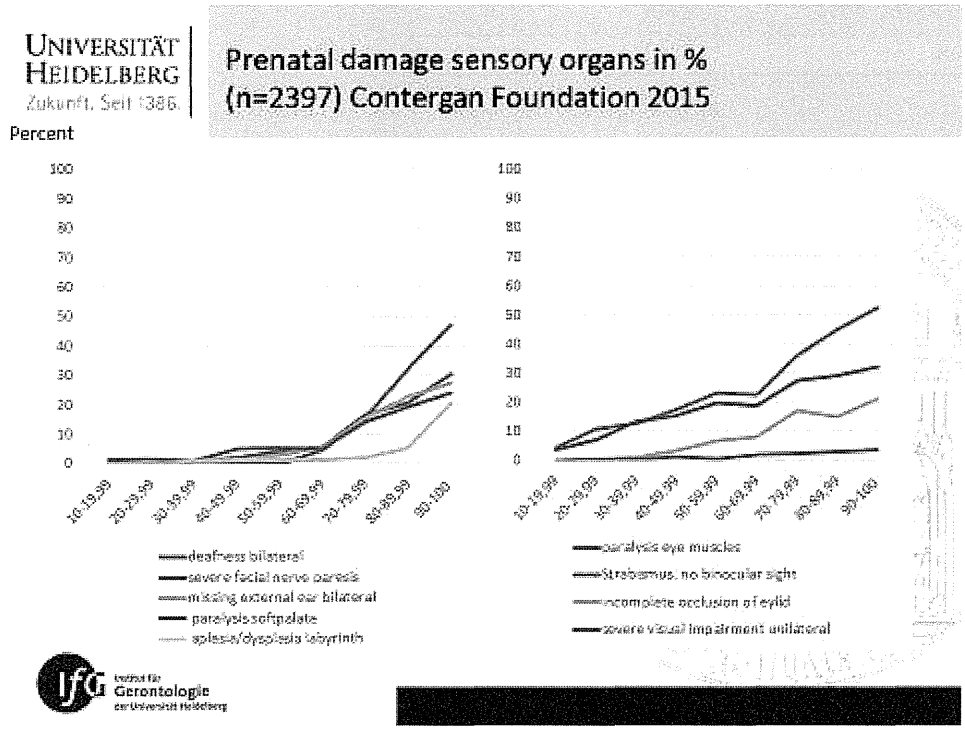

The figure on the left shows the amount of damage in the arms and the spine, the figure on the right shows data concerning damage in the hips and legs both referring to the amount of damage points. A prenatal damage in the spine is found over all groups in about 30 %. Our data in the survey 2012 show that at present about 90 % complain about pain in the spine and show damage caused by physical overstrain.

In the following figure internal organs show a different pattern, the more points affected people have, the higher is the amount of damage.



In the left diagram, e.g. the incidence of undescended testes unilateral or bilateral increases up to an amount of over 20% in the most affected group of participants. This implies childlessness, one of the gravest hardships thalidomiders suffer. In the right diagram severe malformation of the jaw is found in almost one third in the most affected group. Severe cerebral damage which implies that those affected are not able to go to school, is found in up to almost 30 percent in participants with 90 or up to 100 damage points.

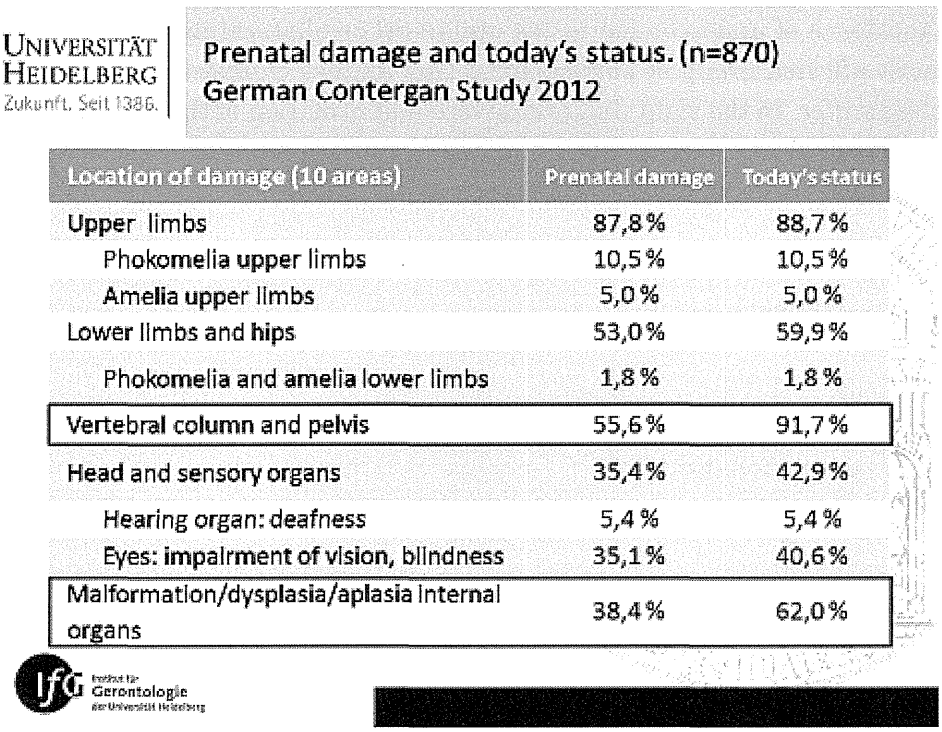
The following figure shows prenatal damage in sensory organs.




The left diagram shows data concerning prenatal malformations in ear, nose and throat. A bilateral hearing loss is found in more than 40 % of severely affected people, the amount starts to increase in the group with 50 to 60 damage points. An aplasia of the labyrinth which causes severe dizziness and restraint of mobility is found in up to 20% of the most affected people.

The right diagram shows different malformations of the eyes and impairment of the eyesight. The most common damage is the paralysis of the eye muscles which can be found all over all groups of participants and increases up to 50% in the groups with the highest amount of damage points. It implies a severe limitation in every day's activities with secondary damage in the spine.

The next figure compares the data collected in the survey of 2012 on prenatal damage of Thalidomide affected people and today's status.




The prenatal status defines the number of the damage points, which measure the dimension of the damage. We wanted to compare the prenatal status to today's physical status. Today's physical status is controlled by 3 components:

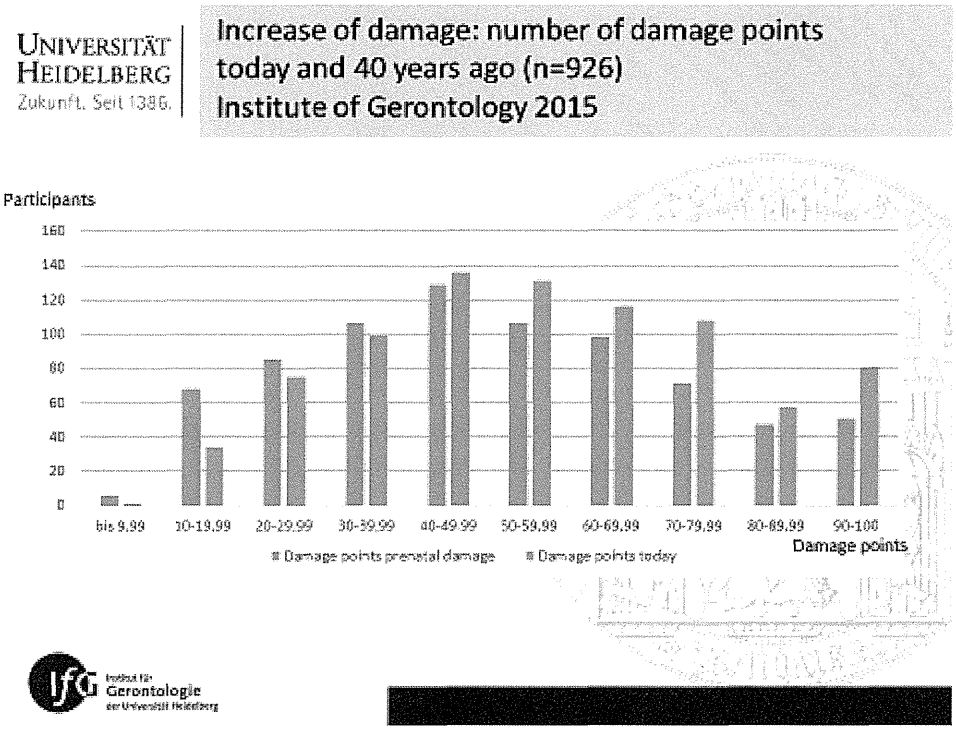
1st: The further development of prenatal damage and the physical impairment depend on physical overstraining.
2nd: The secondary damage develops in areas with no prenatal damage by pathological biomechanical stress due to compensation of restricted mobility.
3rd: The third component are aging processes, which begin to trouble everyone after about the 30th birthday. People without Thalidomide damage do not feel their getting older until the 60th or sometimes 70th birthday. Healthy persons have a lot of biological resources, the more resources, the longer it will last until they feel they are getting physically older. Through detailed questioning we got the impression – though we are not able to measure it – that the population of thalidomiders have only poor resources, therefore they grow older earlier than the general population.

Looking at this figure there is a shift in the amount of people damaged mainly in the spine and in internal organs. The results of our questionnaire concerning the vertebral column with pelvis show in 55 percent a prenatal damage but over 90 percent of the participants complain of discomfort and pain showing severe pathologies. The difference is supposedly caused by overstrain on prenatal damaged organs and/or overstrain and disbalance in healthy organs causing secondary damages.

The spine e.g. is damaged following a disbalance of patterns of movement, caused e.g. by short arms or by arms with different length and different kind of damage which implies asymmetry of movements causing overstrain. Damages in different degrees and locations may develop thus in the course of 50

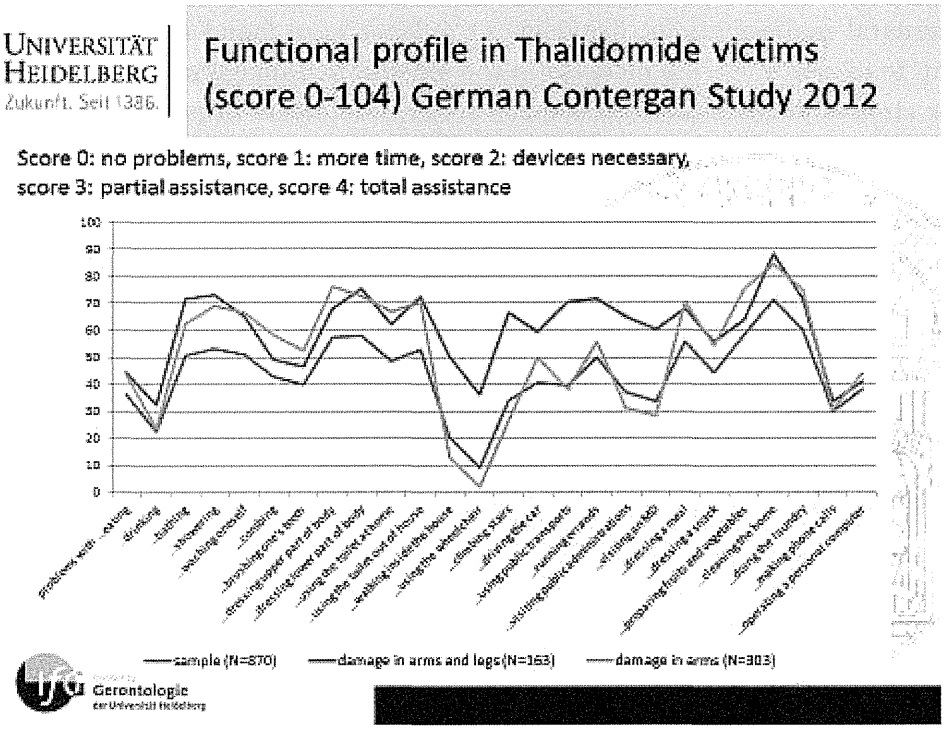
years. In internal organs prenatal malformations, dysplasia or aplasia were found in 38 percent, at present there are found in up to 62 percent. This increase in the amount of damage in this population is due to two factors: better clinical diagnostics with a more efective detection of pathologies and a decline of the capability of compensation in thalidomiders due to an early manifestation of the aging processes.

In the evaluation survey 2015 participants were asked to write down the amount of damage points they had in their first medical exploration 40 or 50 years ago and how many they have at present. In spite of the fact that only prenatal damage gets points, there is a shift in the amount of affected people in the different groups, showing an increase in the groups with a higher amount of points and a decrease in groups with a minor amount of points as can be seen in the following figure.




Prenatal damages were described 40 years ago, but not all of them were detected. Many of them start causing discomfort since 5 to 10 years. Diagnostic methods improve rapidly and clinical results become more accurate.

In the survey of 2012 was established a functional profile of the participants in order to specify the impairments concerning different activities of daily life. In the following figure there are the data of three groups, the overall sample, the participants with damage in the upper limbs and the participants with damage in both upper and lower limbs.




The score ranges from 0 to 104. A low score means a high level of autonomy, a high score stands for a loss of autonomy in different degrees. A participant with a score of e.g. 104 shows no independency, he needs total assistance in all activities.

A score of 0 signifies that the correspondent activity can be realized without any problems. A score of 1 means that the participant needs more time to perform the respective task. With a score of 2 the participant needs special devices to perform the activity. The score of 3 stands for partial assistance, the score of 4 defines total assistance in performing a special activity. The different scores are added to obtain the total individual score.

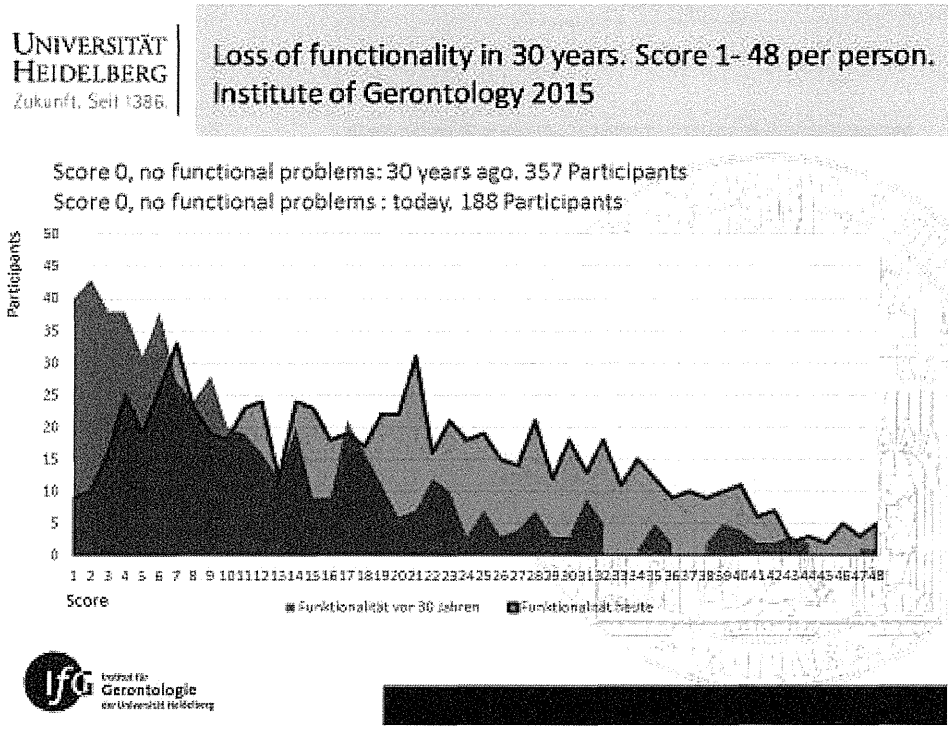
The diagram identifies the different levels of autonomy in the different groups of participants corresponding to activities of daily life e.g. going outside the house, driving the car, running errands, visiting a medical doctor or doing things at home, cleaning or doing laundry or bathing, showering and so on.

In the survey of 2015 the change of functionality was determined in the whole sample. The changes which took place over 30 years were documented in 12 activities of daily living – 30 years ago and at present. The correspondent scores defining the level of autonomy were 0 to 4, the same as in the preceding figure. The data of the following activities were collected and the value of the 12 scores were added to constitute the total individual score.

1. to shower
2. to dress one self
3. to go tot he rest room
4. to walk
5. to climb stairs
6. to do small errands, to go to the doctor
7. to go by public transportation
8. to drive a car

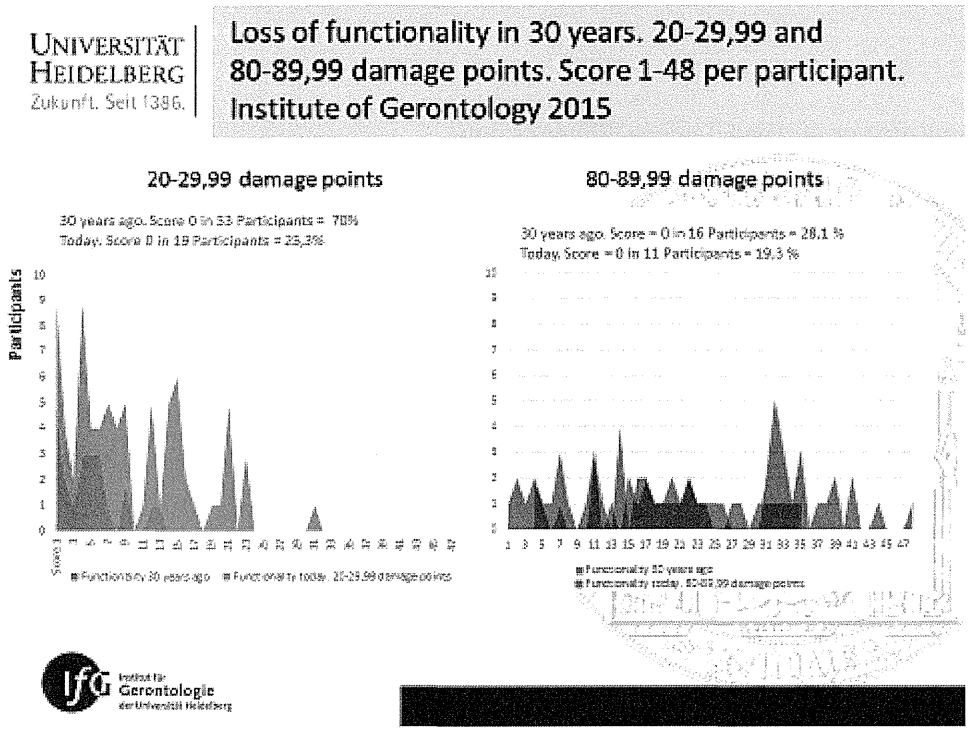
9. to prepare a meal
10. to clean the home
11. to use a telephone
12. to use a personal computer or similar devices 30 years ago.

The functionality of the participants 30 years ago is marked in blue, the functionality at present is marked in red. In this figure the total score of every participant is entered in the diagram, the highest score attained was a score of 48. Every score includes the respective number of participants having attained a score of 1 to 48. A low score means a high grade of autonomy, the higher the score, the more pronounced is the loss of independency.
The score of 0 is not part of the diagram. 357 participants stated to be autonomous 30 years ago in all activities, at present there are left only 188 participants with complete autonomy.



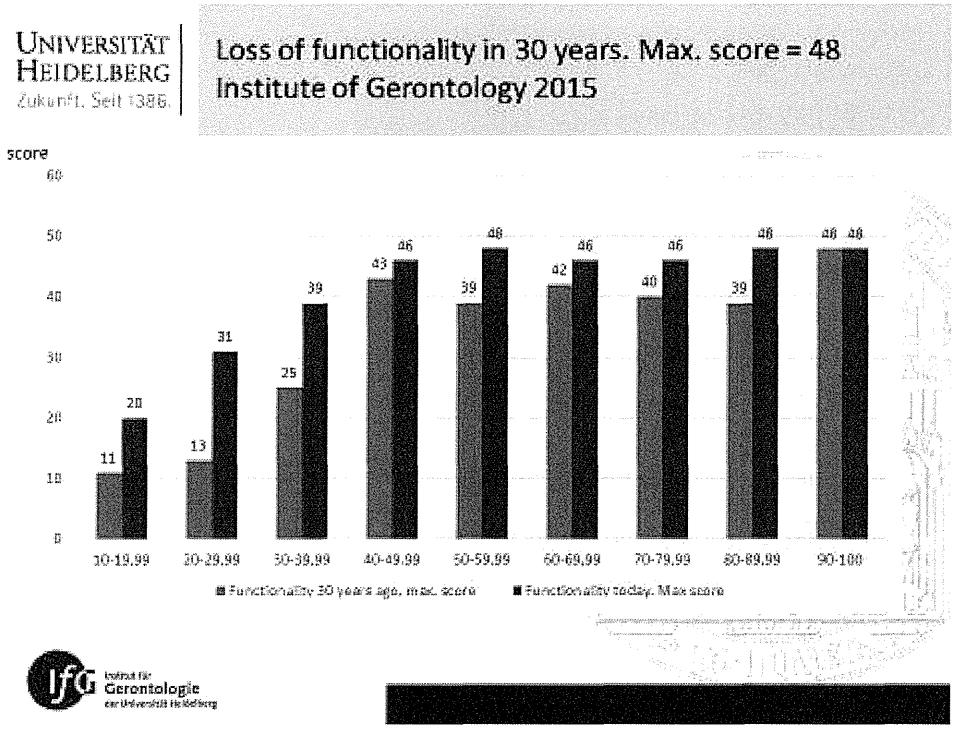

30 years ago there were represented mainly the scores of 1 to 20 or 25. At present a higher amount of affected people have higher scores of 20 to 40. Higher scores are a measure for a loss of functionality and there is a shift to an increasing loss of autonomy in this population over a period of 30 years. This shift in functionality is possibly the expression or measure for the increasingly developing secondary damages and the progressively deterioration of prenatal damages.

In the following picture there are compared two groups of participants, one group with a low amount of points (20-30), another with a high amount of points (80-90). The collected data concerning functionality compare the situation at present with the situation 30 years ago.




There is a bigger loss of functionality in the group of participants with 20 to 30 damage points than in the other group with a high amount of damage points. At present 19 participants are autonomous in all activities, 30 years ago they were 53.
The increase in score points which corresponds to a loss in function is considerable in the participants with low points. They had poor damage, therefore they led an almost normal life, they did a lot of heavy physical work, and they pay a high price for lifelong overstress.
In participants with high damage points there is a loss of function, too, but the amount of this loss is not that big. The participants with a score of 0 diminishes by only 9% in 30 years. There is one person with a score of 48. In this group the autonomy was already diminished 30 years ago, as they suffer from a high amount of severe physical damage of all kinds.

In the following figure the maximum scores reached by participants with different damage points 30 years ago and at present are compared.




The biggest increases in loss of functionality are seen in the participants with low prenatal damage points. Participants with 20 to 30 points show a difference of scores of 18. People with 40 points and more differ not so much concerning their scores if compared through 30 years. We find an increasing homogeneity in this very heterogeneous population. We find this homogeneity in other areas, too, e.g. pain or physical resilience.

The prevalence of pain in the sample of 2012 compared to the data of 2015 show an increase. Data on different dimensions of pain were collected, too, and there could be observed as well a tendency to homogenization.