ESF Exploratory Workshop on
Prevention and Treatment of Vitamin D Deficiency in Europe: Rationale and Design of a Randomized controlled Trial with Moderate and high Doses of Vitamin D3 and Multiple Outcomes

Amsterdam (The Netherlands), 15-17 September 2010

Convened by:
Paul Lips, Natasja van Schoor and Roger Bouillon

SCIENTIFIC REPORT
1. Executive summary

Vitamin D deficiency is common in older persons in Europe. Severe, longstanding vitamin D deficiency may lead to osteomalacia. It also causes secondary hyperparathyroidism, bone loss, osteoporosis and fractures. In recent years it has become clear that the active metabolite of vitamin D is involved in many cellular and metabolic processes. The vitamin D receptor has been found in many organs, and the vitamin D knockout mouse shows many defects outside the skeleton. Vitamin D deficiency has been associated with decreased physical performance and falls, with immunologic abnormalities including auto-immune diseases and decreased resistance to infections. It has been associated with insulin resistance and diabetes type 2, hypertension, cardiovascular diseases, cognitive decline and depression. In addition, vitamin D suppresses proliferation and stimulates differentiation of cells, and vitamin D deficiency has been associated with cancer of colon, breast and prostate. While widespread effects of vitamin D have been suggested in epidemiological studies and knockout mice models, definite proof can only be generated through randomized double-blind clinical trials. Double-blind trials have demonstrated that vitamin D with or without calcium can prevent fractures and falls. With respect to other endpoints such as insulin resistance, cardiovascular disease or depression, only small trials lacking adequate power have been performed, usually with a negative outcome. Some European investigators already came together during the past years to discuss a clinical trial with different doses of vitamin D and with multiple outcomes. A request for funding to the European Science Foundation was made to organize an Exploratory Workshop to discuss the design of a clinical trial with vitamin D3 with the aim to prevent chronic diseases in older persons. The programme was discussed with some experts in the field. The participants of the workshop included clinical researchers, endocrinologists, rheumatologists, a geriatrician, epidemiologists, a psychiatrist, health scientists, a nutritionist. The workshop was organized by Dr Natasja van Schoor and Professor Paul Lips from the VU University Medical Center in Amsterdam, and Professor Roger Bouillon from the Catholic University of Leuven. Professor Bouillon also represented the European Science Foundation. Professor Arie Nieuwenhuizen Kruseman represented the Standing Committee of European Doctors. Both delegates gave a short presentation on the organisation which they represented.

The workshop consisted of short state-of-the-art presentations, followed by long discussions. Most of the time was used to discuss the rationale and design of a randomized double-blind controlled clinical trial with different doses of vitamin D to prevent chronic diseases in older persons. Classical outcomes of vitamin D deficiency such as osteoporosis, falls and fractures were discussed with the emphasis on what was not known, e.g. whether higher vitamin D doses than 800 IU/d confer additional benefit compared to lower doses with regard to falls and fractures. Non-classical outcomes were discussed extensively, including sarcopenia and physical performance, insulin resistance, metabolic syndrome and diabetes mellitus type 2, cardiovascular diseases, pulmonary diseases, infectious diseases and cancer, depression and cognitive decline. Threshold levels of 25-hydroxyvitamin D indicating the level above which more vitamin D would not have an additional benefit, were discussed. The threshold might be different for different outcomes. The clinical trials on the effect of vitamin D in older persons, currently going on worldwide, were reviewed. It was concluded that only some trials were addressing more than one outcome. Only one trial in the USA with a wide range of outcomes was identified. The role of calcium intake and supplementation in vitamin D trials was discussed. Most trials that demonstrated a preventative effect of vitamin D on fractures also used a calcium supplement. However, calcium may also have side effects. The economic burden of vitamin D deficiency can only be roughly estimated as long as the true effects of
vitamin D on cardiovascular disease and cancer are not well known. The effects of vitamin D supplementation may be influenced by polymorphisms (variants) of the vitamin D receptor gene and the vitamin D binding protein gene. Incidences of insulin resistance, diabetes type 2, cardiovascular diseases, infectious diseases, cancer and depression were discussed to enable sample size calculations for a vitamin D trial with multiple outcomes. The gold standard for estimation of serum concentrations of 25-hydroxyvitamin D was discussed and decided to be tandem mass spectrometry.

Most time was spent on discussing the design of a randomized double-blind placebo-controlled trial with various doses of vitamin D and multiple outcomes. This discussion was led by Cyrus Cooper.

This trial should include persons of 70 years and older, preferably similar or higher numbers in older age groups, e.g. 70-74 years 1500 persons, 75-79 years 1500 persons or more and 80+ 1500 persons. In the higher age groups, persons are more likely to be vitamin D deficient, and the number of events for most outcomes is higher than in younger age groups. Exclusion criteria would be immobilisation on one side and a very active outdoor life on the other side. Besides the classical outcomes osteoporosis, falls and fractures, non-classical outcomes were discussed. It was decided to include novel outcomes such as physical performance, insulin resistance, cardiovascular events, peak expiratory flow, respiratory infections, depression, cognitive decline, and composite endpoints as were used in the Women’s Health Initiative. The use of one or two doses of vitamin D against placebo was discussed, as well as the use of two doses of vitamin D without placebo group. It was decided that a low and a high dose of vitamin D, 800 and 2000 IU/d should be compared with a placebo group. It should be known whether a higher dose results in a better response. At baseline and at one year, blood samples should be obtained for the measurement of 25-hydroxyvitamin D and safety parameters. Other variables, such as bone mineral density, joint radiographs, should be assessed in subgroups. Eleven centres were volunteering to include participants in the trial, making a total number of 5000 feasible. It was decided to submit a proposal to the European Union FP7 Health programme. This is a two-stage procedure with a first deadline on October 13 and a second deadline in February. The workshop was concluded with discussion on follow-up activities.

2. Scientific content of the event

The meeting started on September 16th and was opened by Paul Lips. The ESF representative Professor Roger Bouillon (ESF Standing Committee for the European Medical Research Councils) presented the aim and function of the European Science Foundation, and how the ESF stimulates collaborative research.

The morning was devoted to the classical and non-classical consequences of vitamin D deficiency and the ongoing international vitamin D trials. Paul Lips presented an overview of the skeletal consequences of vitamin D deficiency, osteomalacia, osteoporosis and fractures. Vitamin D deficiency is associated with osteoporosis and fractures, and thresholds for bone turnover parameters and bone mineral density were observed in the Longitudinal Aging Study Amsterdam at a serum 25-hydroxyvitamin D concentration of 40 and 50 nmol/l respectively. Randomized clinical trials have demonstrated that vitamin D 400-800 IU/day usually combined with calcium 1000 mg/day can prevent 10 to 20 % of fractures in older persons. The lively discussion focussed on whether vitamin D should be combined with calcium, or should be given alone, and secondly whether a higher dose than 1000 IU/day would be better, and whether a linear dose-relationship would exist. Calcium supplementation might be
harmful for cardiovascular outcomes as was shown in a recent meta-analysis. Another issue was compliance and the targeting to the right population. Meta-analyses showed that trials with higher compliance and trials in the institutionalized had better outcomes. Higher doses lead to a quicker normalisation of serum 25(OH)D levels. A recent trial comparing 800 and 1600 IU/day did not show differences in musculoskeletal outcomes.

The outcomes sarcopenia and physical performance were presented by Marjolein Visser. She discussed sarcopenia, i.e. loss of muscle mass, and dynapenia, i.e. loss of muscle strength. The latter may be more important regarding the outcome physical performance. The discussion centered on outcome measures, the most simple being the short physical performance battery of Guralnik. There is discussion on the thresholds for muscle mass and strength. A European proposal was published in Age & Ageing, including a stepwise definition. It was agreed that proximal muscle strength is an important outcome criterion. It can be measured by tests (e.g. chair stands) or by dynamometers.

Witte Hoogendijk presented an overview of depression and cognitive decline. Minor depression and major depression both are well defined and associated with vitamin D deficiency. The serum parathyroid hormone concentration is also associated with depression, so vitamin D deficiency could either directly or indirectly through secondary hyperparathyroidism cause depressive symptoms and depression. Depression will be a very novel outcome of any clinical trial with vitamin D.

Roger Bouillon presented available data on the association between vitamin D and cancer. In vitro studies showed that vitamin D suppresses cell proliferation and stimulates cell differentiation. Animal data point to the same direction. Epidemiological studies show associations between latitude and cancer and between vitamin D deficiency and cancer. In addition, associations between vitamin D intake, serum 25-hydroxyvitamin D levels and colon, breast and prostate cancer have been observed. However, intervention studies were either negative or inadequately powered to show positive results.

Natasja van Schoor explored the clinical trial register and summarized vitamin D trials either with one or with multiple outcomes that are currently going on. The main question in the ensuing discussion was what would be new in the trial that we will propose. New points are the size of the trial, novel outcomes, different dosages (moderate and high), and the interaction with genetics and comedication.

Professor Arie Nieuwenhuizen Kruseman presented the activities of the Standing Committee of European Doctors CPME (Comité Permanent des Médecins Européens).

Haakon Meyer discussed the required blood levels of 25-hydroxyvitamin D based upon different thresholds. He started with the position statement of the International Osteoporosis Foundation. The majority of the IOF Working Group concluded the optimal serum 25-hydroxyvitamin D level was 75 nmol/l or higher. For older adults the level should be at least 60 nmol/l. The regression curve between vitamin D and cancer and other outcomes such as mortality could be U shaped, with increased cancer incidence with very low and very high levels. The discussion on required levels centered around differences in assay techniques, leading to interlaboratory variation up to 30%. Using a central laboratory facility would eliminate this problem. Most attendees were in favour of central measurement of serum 25-hydroxyvitamin D by tandem mass spectrometry (LC-MS/MS). There are few data on the achieved levels of 25-hydroxyvitamin D with higher doses of vitamin D3. The increase of serum 25-hydroxyvitamin D with increasing doses is non-linear. The whole mechanism is to protect against too much vitamin D.
Paul Lips introduced the discussion on the planned multicenter trial with vitamin D and multiple outcomes. The doses of vitamin D of vitamin D could be the currently recommended dose 400-600 IU/d versus a high dose 1600-2000 IU/d. Alternatively, a placebo group could be compared with a moderate dose, 800 IU/d, and a high dose 2000 IU/d. In the latter case, all participants would be allowed to take a vitamin D supplement up to the recommended dose (usually 400 IU/d). Another point is the addition of a calcium supplement. Multiple outcomes could include osteoporosis and fractures, physical performance and falls, peak expiratory flow and respiratory infections, insulin resistance, metabolic syndrome and diabetes type 2, cardiovascular diseases, depressive symptoms and cognitive decline. Another point was selection of vitamin D deficient participants by screening of blood levels or just screening on probable vitamin D deficiency, e.g. not coming outside, low sun exposure.

The round of comments by all participants and the general discussion were led by Cyrus Cooper. He raised as first point whether the trial should be explanatory or pragmatic.

The following points were mentioned:

**Armin Zitterman**: targeted to vit D insufficiency, 2 doses of vit D vs placebo, many outcomes including mortality.

**Elena Kamycheva**: a placebo group should be included; outcome inflammation, mortality

**Haakon Meyer**: no selection criteria; placebo/low dose D/high dose D.

**Christel Lamberg Allardt**: no selection; 70-80 years; a placebo group is desirable; outcomes mortality and infections.

**Marjolein Visser**: an explanatory trial should include everybody, while a pragmatic trial should include deficient people. Two groups of vit D; multiple outcomes including falls and physical function.

**Harald Dobnig**: the trial should be explanatory and targeted at vit D deficient persons (25(OH)D < 50 nmol/l); vit D 400 vs 2000 IU/d; calcium 500 mg/d should be given to everybody; outcomes: infections, days of bedrest, hospital days, mortality; 3 yr follow-up.

**Natasja van Schoor**: 3 treatment arms requires higher numbers.

**Joyce van Meurs**: for genetics, 2 treatment groups is better than 3.

**Roger Bouillon**: an explanatory trial is better than a pragmatic trial; however a pragmatic trial fits with the FP7 call; the addition of calcium is impractical (compliance is a problem). Novel outcomes are insulin sensitivity, (respiratory) infections, depression, physical performance, osteoarthritis, pain.

**Marieke Snijder**: the trial should be explanatory, but FP7 requires a pragmatic trial. No selection criteria; more primary outcomes.

José Manuel Quesada: the trial should be pragmatic and realistic; vitamin D should be measured in all participants; 3 groups: placebo vs low dose vs high dose; calcium 1000 mg/d.

**Steven Boonen**: two groups; usual care vs 2000 IU/d. Target: low vit D status and this is more common in age group 75+; outcomes: musculoskeletal; physical function; infections; mortality.

**Arie Nieuwenhuizen Kruseman**: Pragmatic trial; placebo control if ethically acceptable; multiple outcomes. Two or 3 groups: (0) vs 800 vs 2000 IU/d.

**Jan Stepan**: target: low serum 25(OH)D < 50 nmol/l; 2 groups: usual care vs 2000 IU/d; no routine calcium supplement, but measure calcium intake. Outcomes: falls, fractures, ΔPTH.

**Witte Hoogendijk**: No selection based on 25(OH)D levels; 3 groups: usual care (placebo), 800 and 2000 IU/d.

**Silvano Adami**: prefers a pragmatic trial; secondary endpoints can be explanatory; 400 IU/d vs 2000 IU/d. Outcomes: falls, fractures, infections.
Most participants were in favour of 3 treatment arms (placebo/800/2000). However from a genetic point of view less treatment arms with more participants per arm were preferred. Selection criteria should be as few as possible, apart from age. As novel outcomes were considered depression, insulin sensitivity, proximal muscle strength/functional parameters, osteoarthritis/pain, (respiratory) infections, comorbidity index (see Women’s Health Initiative), quality of life (EQ-5D), cost-effectiveness. Ethical points were raised: how to comply with guidelines? The placebo group should have the recommended dose, or everybody should be allowed usual care, i.e. everybody is allowed to take the locally recommended dose (400-600 IU/d). Should the participants be randomized on calcium 500/1000 mg/d or should calcium only be supplemented when calcium intake is very low? The latter choice was selected. Should vitamin D be given once daily, once per week or once per month? If daily calcium supplementation were selected, then vitamin D should also be given daily. Most agreed that it was innovative to select higher age groups. The levels of serum 25-hydroxyvitamin D should be measured locally with central crosscalibration in case of screening on vitamin D deficiency. When screening on serum 25-hydroxyvitamin D is not done, then baseline and treatment levels can be better estimated at the end in a central laboratory by LC-MS/MS. All labs can still send local samples for cross-calibration. The number of centers should be at least 8 with 500 participants per center. Concerning the personnel, two nurses per center would be required during the inclusion phase of the trial and one nurse during follow-up. The discussion on the trial would be continued on September 17.

**Steven Boonen** discussed calcium intake and calcium supplementation in trials for the prevention of fractures. Trials were more often effective when vitamin D was combined with calcium, as follows from meta-analyses. On the other side, calcium supplementation might have an increased cardiovascular risk. However, this is not clear as the data on cardiovascular risk were all obtained from posthoc analyses. Consensus was reached to supplement calcium when calcium intake is low i.e. less than 1000 mg/d, or less than 4 dairy consumptions per day.

**Armin Zitterman** reviewed data on the cost-effectiveness of vitamin D supplementation. The 363 million people in 17 European countries have a gross domestic product of 12 trillion Euro. The total expenditure on health is 9.4%. Three possible scenario’s exist: 1. no cost reduction; 2. 16.2 % of total cost will be saved, i.e. 184 billion; 3. Vitamin D deficiency (serum 25-hydroxyvitamin D<25 nmol/l) occurs in 20 % of the population; 5 % of the costs are related to vitamin D, i.e. 11 billion Euro. A question during the discussion was whether costs per QALY gained could be calculated for vitamin D. Another point was the societal impact versus the individual impact. The impact on mental health costs would be high, if vitamin D would partially protect against depression.

**Joyce van Meurs** reviewed the relationship between single nucleotide polymorphisms and fractures. A SNP of the vitamin D binding protein gene was associated with an increased fracture risk. Concerning the vitamin D receptor gene, only the CDX-2 genotype was associated with fractures in the Rotterdam Study (non-vertebral fractures) and in the GENOMOS consortium (vertebral fractures). The Sunlight consortium studies genetic determinants of vitamin D status. Serum 25-hydroxyvitamin D is determined by vitamin D binding protein gene GC, and the enzyme genes CYP2R1, DHCR7. To study interactions of genetic variants with the effect of treatment on different outcomes, measurement of serum 25-hydroxyvitamin D would also be needed at baseline and the end of the trial. The SNP’s of relevant genes should be examined for interactions with treatment effect. Other SNP’s might
be important for other clinical outcomes. The 1α-hydroxylase gene may be important as well as the 24-hydroxylase gene.

With this presentation and the following discussion, the first day was concluded.

On September 17 Cyrus Cooper started to review the incidence of fractures within different European countries. There are large differences in incidence rates between Nordic countries, Western Europe and the Mediterranean countries. For sample size calculations, the incidence rates of various countries should be used, e.g. Sweden and the UK or the Netherlands. A vertebral radiograph to detect vertebral fractures or a bone mineral density measurement with DXA at baseline and at the end would increase the number of outcomes with a higher power. Risk factors for falls should be recorded as confounders. Which fractures and which falls should be included? All fractures, except skull, hand and foot fractures should be reported. Recurrent falls are more often caused by intrinsic factors while single falls are more often caused by external factors.

Marielle Snijder reviewed incidence data on diabetes and insulin resistance. A clinical cutpoint for insulin resistance is not available. If possible, HOMA should be calculated, and oral glucose tolerance tests at baseline and following treatment could be done in a subset. Concerning sample size calculations, these should be done for hard endpoints such as falls and fractures. For other outcomes, effect sizes should be calculated that can be detected with a given sample size.

Harald Dobnig reviewed the prevalence and incidence of infectious diseases and cancer, and the mortality. The incidences are too low to use cancer as an outcome in most trials unless very large. It would be best to include cancer in a comorbidity index. The Global Health Index as used in the Women’s Health Initiative could be used. The data from vitamin C trials could be used for incidence data of common colds. Prevalence and incidence figures can be found on www.oecd.health/health specific for country and age.

The discussion on the FP7 proposal for the clinical trial was continued, chaired by Paul Lips. According to most participants the trial should be focused on high age e.g. 70-75 yr 1000+ persons; 75-80 yr 2000 persons; 80+ yr 1000+ persons. Stratification should be performed on age and sex. Women and men should be analysed separately, depending on outcome and required power. Immobilized persons should be excluded, but people in residential care can participate. It was decided to randomize into three groups: 1. Placebo; 2. Vitamin D3 800 IU/d; 3. Vitamin D3 2000 IU/d. Participants in all groups will receive a leaflet with local recommendations on vitamin D.

How should sample size be calculated? Cyrus Cooper: The placebo group should be compared to the 2000 IU group. In the analyses group 1+2 can be compared with group 3, or group 1 can be compared with group 2+3. As vitamin D deficiency is less common in the age group 70-75 yr, this group can be smaller, especially when screening on vitamin D deficiency is not done at baseline (Steven Boonen). Anyhow blood samples should be obtained at baseline and kept frozen. Which exclusion criteria should be used? Persons with a high physical activity or a recent sun vacation might be excluded. The FP7 Health call asks for interventions that change clinical practice. This might indicate that vitamin D supplementation should be implemented (Marjolein Visser). The diet of the participants should be assessed, including fish consumption, cod liver oil, fortified milk. The following novel outcomes will be assessed: osteoarthritis, joint space narrowing on knee radiographs in
subset (500-1000 persons), WOMAC questionnaire, physical performance, respiratory infections, disability, metabolic syndrome, quality of life, muscle pain—widespread or fibromyalgia score. Concerning calcium, it is decided to give everybody 500 mg calcium per day unless 4 dairy consumptions are used daily. Blood samples will be obtained at baseline and after 1 year for measurement of 25-hydroxyvitamin D and safety parameters. Serum 25-hydroxyvitamin D will be measured at the end of the study in a central laboratory with LC-MS/MS, either in Leuven (Roger Bouillon/Steven Boonen) or in Cordoba (José Manuel Quesada). Cross-calibration will be done with local laboratories to standardize the assessment of vitamin D status. Safety parameters will be measured at baseline and after 1 year in the local laboratories including calcium, renal and liver function. Christel Lamberg-Allardt focuses the attention to the text of the call “concomitant multimodal therapies”: this might include vitamin D and calcium, and interactions with co-medication. According to Cyrus Cooper the general aim of the vitamin D trial should be to preserve physical function in older people. The participants should receive a leaflet with recommendations on physical activity. The following centres have opted as recruitment centre: Leuven, Bochum, Graz, Oslo, Tromso, Helsinki, Southampton, Prague, Verona, Cordoba, Amsterdam. When each centres would recruit 500 participants, more than 5000 participants could be included. The recruitment could be done by advertisement, residential care centres, general practitioners or by asking addresses from the municipality. All ethnicities will be included.

The budget was discussed: 2 study nurses per centre during recruitment, one thereafter; 0.5-1 PhD student per centre; radiographs, DXA, blood measurements, leaflets, questionnaires, transfer costs.

Follow-up activities: The deadline for the first stage of the two-stage FP7 call is 13 October. A draft application will be circulated in the first week of October. Natasja van Schoor will collect official names of institutes and hospitals, expertise of the centres, and the interest in the work packages. During lunch, further details were clarified. After lunch, the meeting was adjourned.

3. Assessment of the results, contribution to the future direction of the field

Most of the time during the workshop was spent on discussion, and most of the discussion was spent on the design of a randomized double-blind placebo-controlled clinical trial on the effect of different doses of vitamin D on multiple outcomes. The state-of-the-art presentations were short and to the point. All participants enjoyed the discussions as followed from the feedback during and after the meeting.

The main results from this workshop include:

- Current state-of-the-art with regard to proven and possible effects of vitamin D.
- Defining possible aims for vitamin D treatment, especially novel outcomes, such as physical performance, osteoarthritis, peak expiratory flow, respiratory infections, metabolic syndrome and depression.
- Design and feasibility of a large multicentre clinical trial with different doses of vitamin D versus placebo in older persons on classical and novel outcomes of vitamin D treatment and interaction with genetic variants.
- Preparation of a grant application in the FP7 programme on chronic diseases in the elderly.
The first and most urgent aim was the preparation of the grant application, which was submitted in Brussels on October 13. The results of the first stage will become available in the beginning of December 2010.
4. Final programme

**Wednesday 15 September 2010**

Afternoon

19.30 Dinner

**Thursday 16 September 2010**

10.00 – 10.20 Coffee and tea

10.20 – 10.25 Welcome by Paul Lips (Dept of Internal Medicine, VU University Medical Centre Amsterdam, NL)

10.25 – 10.35 Presentation round, all participants.

10.35 – 10.50 Presentation of the European Science Foundation (ESF)
Roger Bouillon (ESF Standing Committee for the European Medical Research Councils - EMRC)

10.50 – 10.55 Classical consequences of vitamin D deficiency: osteomalacia, osteoporosis, falls and fractures
Paul Lips (Dept of Internal Medicine, VU University Medical Centre Amsterdam, NL)

10.55 – 11.15 Sarcopenia and physical performance
Marjolein Visser (Epidemiology, Faculty of Life Sciences, VU Amsterdam)

Non-classical consequences:

11.15 – 11.30 - depression (including prevalence and incidence)
Witte Hoogendijk (Dept of Psychiatry, VU Amsterdam, NL)

11.30 – 11.45 - infectious diseases, cancer, mortality
Roger Bouillon (Laboratory for experimental medicine and endocrinology, Katholieke University Leuven, BE)

11.45 – 12.00 Required blood level of 25-hydroxyvitamin D: different thresholds for different outcomes?
Haakon Meyer (Dept of Epidemiology, Norwegian Institute of Public Health, Oslo, NO) / Paul Lips (Dept of Internal Medicine, VU University Medical Centre Amsterdam, NL)

12.00 – 12.15 Overview randomized controlled trials
Natasja van Schoor (VU University Medical Centre, Amsterdam, NL)

12.15 – 12.25 Discussion

12.25 – 12.30 Arie Nieuwenhuizen Kruseman (Standing Committee of European Doctors)

12.30 – 13.30 Lunch

14.00 – 14.20 Introduction brainstorm “Design of a randomized controlled trial with a moderate and a high dose of vitamin D and a placebo group” (inclusion and exclusion criteria, vitamin D dose, calcium, possible outcomes, follow-up duration)
Paul Lips (Dept of Internal Medicine, VU University Medical Centre Amsterdam, NL)

14.20 – 16.10 Plenary discussion “Design of a randomized controlled trial”
Cyrus Cooper/all participants
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.10 – 16.30</td>
<td>Coffee/tea break</td>
</tr>
<tr>
<td>16.30 – 16.45</td>
<td>The role of calcium and nutrition</td>
</tr>
<tr>
<td></td>
<td><strong>Steven Boonen</strong> (Centre for Metabolic Bone Disease, University of Leuven, BE)</td>
</tr>
<tr>
<td>16.45 – 17.00</td>
<td>Discussion</td>
</tr>
<tr>
<td>17.00 – 17.15</td>
<td>Economic Burden of vitamin D deficiency in Europe</td>
</tr>
<tr>
<td></td>
<td><strong>Armin Zitterman</strong> (Heart and Diabetes Centre North-Rhine Westfalia, Bochum, DE)</td>
</tr>
<tr>
<td>17.15 – 17.30</td>
<td>Discussion</td>
</tr>
<tr>
<td>17.30 – 17.45</td>
<td>Genetics: the role of the vitamin D receptor and vitamin D binding Protein</td>
</tr>
<tr>
<td></td>
<td><strong>Joyce van Meurs</strong> (Erasmus MC, Internal Medicine, Rotterdam, NL)</td>
</tr>
<tr>
<td>17.45 – 18.00</td>
<td>Discussion</td>
</tr>
<tr>
<td>18.00 – 18.30</td>
<td>Toasting to a fruitful collaboration</td>
</tr>
<tr>
<td>19.30</td>
<td>Dinner</td>
</tr>
</tbody>
</table>

**Friday 17 September 2010**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.30 – 8.35</td>
<td>Opening</td>
</tr>
<tr>
<td></td>
<td><strong>Paul Lips</strong> (Dept of Internal Medicine, VU University Medical Centre Amsterdam, NL)</td>
</tr>
<tr>
<td>8.35 – 8.45</td>
<td>Prevalence/incidence of falls and fractures</td>
</tr>
<tr>
<td></td>
<td><strong>Cyrus Cooper</strong> (Dept of Rheumatology, University of Southampton, UK)</td>
</tr>
<tr>
<td>8.45 – 8.55</td>
<td>Prevalence/incidence of insulin resistance, diabetes type 2, cardiovascular diseases</td>
</tr>
<tr>
<td></td>
<td><strong>Marieke Snijder</strong> (Dept of Health Sciences, VU Amsterdam, NL) / <strong>Natasja van Schoor</strong> (VU University Medical Centre, Amsterdam, NL)</td>
</tr>
<tr>
<td>8.55 – 9.05</td>
<td>Insulin resistance, diabetes type 2, cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>Presentation of slides of Bess Dawson Hughes (Tufts University Centre of Ageing, Boston, US)</td>
</tr>
<tr>
<td>9.05 – 9.15</td>
<td>Prevalence/incidence of infectious diseases, cancer, mortality</td>
</tr>
<tr>
<td></td>
<td><strong>Harald Dobnig</strong> (Dept of Internal Medicine, Medical University Graz, AT)</td>
</tr>
<tr>
<td>9.15 – 9.30</td>
<td>Discussion</td>
</tr>
<tr>
<td>9.30 – 10.15</td>
<td>Continuation discussion “Design of a randomized controlled trial with a moderate and a high dose of vitamin D and a placebo group” (measurements, estimated effect sizes, sample size)</td>
</tr>
<tr>
<td></td>
<td><strong>Paul Lips</strong>/all participants</td>
</tr>
<tr>
<td>10.15 – 10.45</td>
<td>Coffee/tea break</td>
</tr>
<tr>
<td>10.45 – 11.15</td>
<td>Continuation discussion on randomized trial</td>
</tr>
<tr>
<td>11.15 – 11.30</td>
<td>Gold standard for vitamin D metabolites (mass spectrometry)</td>
</tr>
<tr>
<td></td>
<td>Presentation of slides of Anthony Norman (Dept of Biochemistry, University of California, US)</td>
</tr>
<tr>
<td>11.30 – 12.45</td>
<td>Follow up activities</td>
</tr>
<tr>
<td>12.45 – 13.00</td>
<td>General comments by ESF Representative Roger Bouillon</td>
</tr>
<tr>
<td>13.00 – 14.00</td>
<td>Lunch, informal discussion, closure of meeting</td>
</tr>
</tbody>
</table>
5. Statistical information on participants

Countries
Belgium 2
United Kingdom 1
Norway 2
Finland 1
Germany 1
Austria 1
Czech Republic 1
Italy 1
Spain 1
Netherlands 5 (+1 partial)

Including 4 junior scientists

Representatives of international organisations
Representative ESF 1 (double function)
Representative CPME 1

Gender
Men 12
Women 6

Cancellations 2 (1 woman, 1 man)
6. Final list of participants

Convenor:
Prof. dr. P. (Paul) Lips (M), VU University Medical Center, Endocrinology, The Netherlands, p.lips@vumc.nl
Expertise: endocrinology, vitamin D, classical effects, diabetes

Co-convenors:
Dr. N.M. (Natasja) van Schoor (F, young investigator), VU University Medical Center, EMGO Institute for Health and Care Research, The Netherlands, nm.vanschoor@vumc.nl
Expertise: epidemiology, vitamin D, classical effects

Prof. R. (Roger) Bouillon (M), University Leuven, Laboratory for Experimental Medicine and Endocrinology, Belgium, roger.bouillon@med.kuleuven.be
Expertise: pathophysiology of vitamin D deficiency, classical and non-classical effects, estimation of vitamin D metabolites

Participants:
Prof. W.J.G. (Witte) Hoogendijk (M), VU University, Psychiatry, The Netherlands, witteh@ggzba.nl
Expertise: psychiatry, depression, vitamin D

Prof. dr. A. (Arie) Nieuwenhuizen Kruseman, University Hospital Maastricht, Department of Internal Medicine, division Endocrinology, The Netherlands, a.kruseman@intmed.unimaas.nl
Representative of Standing Committee of European Doctors (CPME)

Dr. Ir. M.B. (Marieke) Snijder (F, young investigator), VU University, Health Sciences, The Netherlands, m.b.snijder@amc.uva.nl
Expertise: adiposity, blood pressure, vitamin D, falls, nutrition

Dr. J.B.J. (Joyce) van Meurs (V), Erasmus MC Rotterdam, Internal Medicine, The Netherlands, j.vanmeurs@erasmusmc.nl
Expertise: genetics, vitamin D receptor, vitamin D binding protein

Prof. dr. M. (Marjolein) Visser (V), VU University Medical Center, Epidemiology, The Netherlands, marjolein.visser@falw.vu.nl
Expertise: sarcopenia, nutrition, life-style

Prof. S. (Steven) Boonen (M), University Leuven, Center of Metabolic Bone Disease, Belgium, steven.boonen@uz.kuleuven.ac.be
Expertise: geriatrics, vitamin D, classical effects, trials
Prof. A. (Armin) Zittermann (M), Department of Thoracic and Cardiovascular Surgery, Heart and Diabetes Center North-Rhine Westfalia, Ruhr University Bochum, Germany, guezit@web.de; azitterman@hdz-nrw.de
Expertise: economic burden of vitamin D deficiency, cardiovascular disease, classical effects

Prof. C. (Cyrus) Cooper (M), University of Southampton, Rheumatology, Southampton, UK, cc@mrc.soton.ac.uk
Expertise: epidemiology, vitamin D, classical effects

Prof. H.E. (Haakon) Meyer (M), Norwegian Institute of Public Health, Epidemiology, Oslo, Norway, haakon.meyer@fhi.no
Expertise: epidemiology of vitamin D deficiency, nutrition

Dr. E. (Elena) Kamycheva (F), Department of Gastroenterology and Nutrition, University Hospital North Norway, Tromso, Norway, elena.kamycheva@unn.no
Expertise: vitamin D, parathyroid function, insulin sensitivity, heart disease

Dr. C. (Christel) Lamberg-Allardt (F), Department of Food and Environmental Sciences, University of Helsinki, Finland, christel.lamberg-allardt@helsinki.fi
Expertise: nutrition, vitamin D classical and non-classical effects, calcium and phosphate

Prof. H. (Harold) Dobnig (M), Department of Internal Medicine, Division of Endocrinology and Nuclear Medicine, Medical University Graz, Austria, harald.dobnig@meduni-graz.at
Expertise: endocrinology, vitamin D, classical and non-classical effects, genetics

Prof. J. (Jan) Stepan (M), Faculty of Medicine, Charles University, Prague, Czech Republic, endojs@seznam.cz
Expertise: estimation of vitamin D metabolites, bone turnover parameters

Prof. S. (Silvano) Adami (M), Rheumatology Unit, Dept of Medicine, Ospedale Maggiore, Verona, Italy, silvano.adami@univr.it
Expertise: vitamin D, classical effects, trials

Prof. J.M. (Jose Manuel) Quesada (M), Endocrinology Unit, Hospital Regional Universitario Reina Sofia, Cordoba, Spain, md1qugoj@uco.es; jmquesada@uco.es
Expertise: vitamin D, classical and non-classical effects, estimation of vitamin D metabolites

Cancellations (due to illness):
Prof. B. (Bess) Dawson-Hughes (F), Tufts University Center for Aging, Bone Metabolism Lab, Boston, USA, bess.dawson-hughes@tufts.edu – nutrition, epidemiology, vitamin D, classical effects, diabetes, vitamin D thresholds

Prof. A.W. (Anthony) Norman (M), University of California, Department of Biochemistry, Riverside, USA, anthony.norman@ucr.edu – vitamin D, classical and non-classical effects, vitamin D receptor, vitamin D binding protein