PROJECT FINAL REPORT

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[1] Usually the contact person of the coordinator as specified in Art. 8.1. of the Grant Agreement.

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1. Final **publishable** summary report

1.1. Executive summary

DO-HEALTH is the largest European Aging study, which tested 3 simple public health strategies (Vitamin D, Omega-3 fats, home exercise program) to extend healthy life expectancy. DO-HEALTH project, started in 2012, is led by the University of Zurich and involves 20 partners: http://do-health.eu/wordpress/partners/.

DO-HEALTH randomised-controlled trial recruited a total of 2'157 men and women age 70 years and older from 7 University Centers in 5 European countries: 552 from Zurich, 253 from Basel, 201 from Geneva, 350 from Berlin, 200 from Innsbruck, 300 from Toulouse, and 301 from Coimbra.

DO-HEALTH established standardized yearly visits in the trial Centers including blood and urine collection as well as extensive objective assessments of all key organ functions (heart, brain, muscle, bone, immunity, vision, glucose-metabolism, kidney, liver) plus 3-monthly in person phone calls visits and constituted a unique data pool and biobank. The last clinical visit after a 3-year follow-up of all participants took place in 11-2017.

DO-HEALTH participants were extensively phenotyped with standardized assessments of multiple organ functions at the objective, subjective and cellular level, health behaviours, functionality, muscle mass, quality of life and incident frailty. The data collected were analyzed to determine the effects of the three interventions on five primary outcomes: fracture risk, lower extremity muscle function, cognitive function, blood pressure, and rate of infections.

DO-HEALTH is the first study to provide an indication that there is a therapeutic range for vitamin D (25-Hydroxyvitamin D) blood levels for several health outcomes: not too little, and not too much.

DO-HEALTH is also among the few studies, which address the long-term use of omega-3-fatty acids, and its effects with regards to five primary health domains: cardio-vascular, bone, muscle, brain, and immunity. Moreover, DO-HEALTH provides data on the long-term effect of omega-3 fatty acids against placebo and combined with vitamin D and/or exercise. The cost-benefit of the 3 interventions individually and combined as a multi-modal intervention was established.

Besides, DO-HEALTH yields important scientific and public health breakthroughs, guiding the establishment of daily nutritional recommendations for vitamin D and omega-3 fats among community-dwelling adults age 70 and older, and with regard to five health domains. DO-HEALTH also defined laboratory reference ranges for a large set of common laboratory markers which are missing today for adults age 70 and older, and of future preventive and therapeutic measures.

In addition, DO-HEALTH developed innovative tools which have a potential for exploitation, such as a practical tablet computer-based direct data entry system designed for clinical trials and clinical practice targeting older adults, an interactive software tool for the broad public and health professionals on how DO-HEALTH findings can be translated into personal use, a health economic model to assess the cost-benefit of interventions targeted at older adults and a FRAX fall-extension model (inclusion of fall in the WHO FRAX algorithm) to enhance absolute fracture risk prediction.

Also, DO-HEALTH established an extensive biobank of more than 200,000 blood samples to support future research on healthy aging with respect to novel biomarkers and treatment development.

1.2. Summary description of project context and objectives

1.2.1 Context (State of Art at the project start, Key challenges)

The global population is ageing (1). The number of European adults aged 70 and older is predicted to increase by 40% by 2030 (2-6), as will the number of adults with age-related chronic diseases (7, 8). Thus, therapeutic interventions that are effective, affordable, and well-tolerated in the prevention of chronic disease at older age are urgently needed and will have an outstanding impact on public health as a whole. Among the most promising interventions that meet these requirements are vitamin D, marine omega-3 fatty acids, and physical exercise. However, their individual and combined effects have yet to be confirmed in a large clinical trial as stated by the 2010 European Parliament Hearing on Vitamin D, and others (9-11).

The 2010 Hearing on Vitamin D recognized broad deficiency of vitamin D: 50% of adults had 25-hydroxyvitamin D (25[OH]D) threshold level below 50 nmol/l, and 70% below 75 nmol/l (9). Notably, in the European SENECA study 36% of senior men and 47% senior women had 25(OH)D serum concentrations below 30 nmol/l, which is consistent with findings from more recent studies (12-16). Vitamin D deficiency with 25(OH)D blood levels below 30 to 50 nmol/l are a major public health concern due to evidence from large cohort studies suggesting an increased risk of several age-related diseases, such as cardiovascular-disease, fractures, falls, dementia, and gastro-intestinal cancer (17) (18-20).

Adults age 70 and older are particularly vulnerable for vitamin D deficiency because of an age-related decline in the skin-based production of vitamin D in response to solar radiation, and their avoidance the direct sun exposure (21-23). Also, dietary sources of vitamin D are rare and largely limited to fatty fish, fish liver oil, and egg yolk (24). 800 IU vitamin D per day, the dose that is recommended today for the prevention of falls (25-28), and fractures (29) among older adults at risk of vitamin D deficiency translate into more than one fish meal daily (fatty fish such as salmon), let alone a higher dose of 2000 IU vitamin D per day, which has been suggested as desirable dose for multiple health endpoints (17). Similarly, low omega-3 fat intake and lack of exercise are acknowledged public health concerns at the European level and especially in among the older adult population (7, 8, 30). Notably, despite the recognition of broad deficiency of vitamin D, omega-3 fats, and exercise, broad public recommendations cannot be substantiated to date because definitive data on health benefits and risks of the 3 interventions individually or in combination are lacking.

Clinical trials frequently exclude adults age 75 and older, or adults who classify as pre-frail (31), especially in the field of cardiovascular disease (32), osteoarthritis (33), and cancer (34, 35). Furthermore, impaired cognitive function has been a concern among older trial participants as adherence to the study intervention may be decreased and adverse events such as falls tend to be forgotten (36). As the older adult segment of the population growing, as is their large share of morbidity and mortality from acute and chronic diseases, their exclusion from clinical trials is a major threat to public health (2-6). Thus, as practiced in DO-HEALTH, inclusion of older adults in clinical trials is justified and urgently needed.

1.2.2 Objectives of the project

The goal of DO-HEALTH is to extend healthy life expectancy by delaying physiologic aging at multi-organ sites in European adults and to reduce healthcare costs via the implementation of effective and broadly applicable disease prevention interventions.

DO-HEALTH was designed to establish evidence for the role of vitamin D, omega-3 fatty acids, and a simple exercise program, both individually and as a combined intervention, in chronic disease prevention at older age, within a 3-year large multi-centre clinical trial enrolling 2'157 community-dwelling men and women aged 70 and older, when chronic diseases increase substantially.

Scientific objectives

- ✓ To test whether 2000 IU vitamin D reduces the risk of chronic disease in community-dwelling adults age 70+ compared to placebo
- ✓ To test whether 1 gram of marine omega-3 fatty acids (EPA+DHA) reduces the risk of chronic disease in community-dwelling adults age 70+ compared to placebo
- ✓ To test whether a well-defined home exercise program (30 minutes 3 times per week) reduces the risk of chronic disease in community-dwelling adults age 70+ compared to control (joint mobility exercise performed 30 minutes 3 times a week)
- ✓ To test whether there is an additive value of the 3 interventions combined as a multi-modal intervention in the reduction of chronic disease in community-dwelling adults age 70+
- ✓ To assess the comparative effectiveness of the interventions and to test whether and to what degree adherence modulates the effect of the 3 interventions on risk reduction of chronic disease in community-dwelling adults age 70+
- ✓ To test whether subgroups of the senior population (by gender, age (70-80, 80-89, 90+), body mass index, baseline physical activity, baseline serum 25-hydroxyvitamin D levels, baseline PUFA levels, previous fall, previous fracture, FRAX –estimated absolute fracture risk, baseline clinical knee OA, and baseline calcium and protein intake) have a differential benefit from the 3 interventions regarding risk reduction of chronic disease
- ✓ To assess the cost-benefit of the 3 interventions individually and if combined as a multi-modal intervention based on an objective health economic model
- ✓ To improve medical care of community-dwelling adults age 70+ by establishing laboratory reference ranges for a large set of common laboratory markers (which do not exist today) and by extending the WHO FRAX fracture prediction model by the risk of falling
- ✓ To validate novel biomarkers of bone and muscle functionality and immunity based on their response to the 3 DO-HEALTH interventions and based on the incidence of musculoskeletal and immunity endpoints of DO-HEALTH

Technical/technological objectives

- ✓ To advance the state of the art in clinical trial data collection and management by creating a complete system that collects, verifies, safeguards, and provides status more easily and efficiently than existing systems
- ✓ To design an animated and motivational exercise instruction video tool for the DO-HEALTH exercise intervention, which –after DO-HEALTH– can be translated into clinical practice as an evidence-based home exercise strategy (a paper version will also be created)
- ✓ To design a practical web-based and interactive software tool for the broad public and health care professionals that will explain how organ-specific DO-HEALTH findings (i.e. heart and muscle health) can be translated to a personal use illustrating the potential benefit of one, two, or all 3 interventions tested in DO-HEALTH
- ✓ To develop a DO-HEALTH health economic computer model simulating the relationship between the 3 interventions and health outcomes. The model will be designed to allow other interventions to be evaluated based on the known relationships between modular variables and health outcomes. This will enable manufacturers of functional foods or pharmaceutical industry to test their assumptions before engaging in expensive outcomes studies.

1.3. Description of the main S&T results/foregrounds

1.3.1 DO-HEALTH Trial met its recruitment and follow-up goals

DO-HEALTH reached 100% recruitment in November 2014, and full completion of follow-up visits in November 2017!

DO-HEALTH RCT successfully recruited 2'157 participants from 7 University Centers in 5 European countries: 552 from Zurich, 253 from Basel, 201 from Geneva, 350 from Berlin, 200 from Innsbruck, 300 from Toulouse, and 301 from Coimbra.

Over the course of the three-year clinical trial, the DO-HEALTH study required the participants to complete a simple home exercise program three times a week and to take supplements of vitamin D and/or omega 3 and/or placebo.

DO-HEALTH participants were followed over the three years by yearly comprehensive clinical visits (baseline visit, 1-, 2- and 3-year follow-up visit) and 3-monthly phone calls (at month 3, 6, 9, 15, 18, 21, 27, 30 and 33).

The last participant last visit took place in November 2017.

Over the three-year course of the trial, only 320 out of 2'157 participants dropped out of the study. The drop-out participants were still invited to attend the last clinical visit, and 63 of them accepted to come to the T3 visit.

Thus, for DO-HEALTH, 2'157 participants were recruited and:

- ✓ 2'157 participants (100%) had a baseline visit,
- ✓ 1'957 participants (90%) had a one-year follow-up visit,
- ✓ 1'861 participants (86%) had a two-year follow-up visit,
- ✓ 1'900 participants (88%) had a three-year follow-up visit.

DO-HEALTH participants are extensively phenotyped with standardized assessments of multiple organ functions at the objective, subjective and cellular level, health behaviours, functionality, muscle mass, quality of life and incident frailty. *DO-HEALTH dataset gathers complete information on function, diet, physical activity, medication use, comorbidities, socio-economic status, joint pain and life style as well as biological markers.* DO-HEALTH is unique in its detailed and repeated comprehensive assessment of overall health and multiple individual organ functions of the participants, including data on all key parameters of bone and muscle health. These data can then be assessed in relation to fall and fracture risk, but also cognitive function, reaction time, and other co-morbidities.

A series of analyses were performed to highlight the characteristics of DO-HEALTH participants at baseline (e.g., prevalence of sarcopenia, frailty and their relationship with cognitive health, health disparities in Europe), and to clarify the role of DO-HEALTH interventions on the 5 primary endpoints.

DO-HEALTH is a success with regards to scientific and public health breakthroughs, but also with regards to technological inventions which have a potential for a commercial exploitation!

As a consequence, the quantitative and qualitative results must be kept temporarily confidential until protection of DO-HEALTH exploitable results and publications. However, here we describe the project's achievements which to date, do not jeopardize DO-HEALTH Intellectual property.

1.3.2 Characterisation of DO-HEALTH participants at baseline

At baseline, **42 Percent of all DO-HEALTH participants are healthy agers**: Data from the first DO-HEALTH clinical visit at study entry show that 42 percent of all DO-HEALTH participants are "healthy agers" – adults who have no chronic illnesses and enjoy good physical and mental health. However, the percent of healthy agers at the start of DO-HEALTH varies between the five countries: in Switzerland (Zurich, Basel, Geneva) 51 percent are healthy agers, in Germany (Berlin) 38 percent, in Austria (Innsbruck) 58 percent, in France (Toulouse) 37 percent, and in Portugal (Coimbra) 9 percent. The factors mediating the Health disparities in Europe as observed in DO-HEALTH were investigated and a manuscript will be published soon.

1.3.3 Evidence on the role of vitamin D and omega-3 fats for the prevention of organ-specific function and chronic disease

The study medication was produced specifically for DO-HEALTH and consisted of Vitamin D3 and/ or Omega 3 fatty acid and/or placebo (high oleic sunflower oil) combined in a soft gel capsule. Each active capsule contained 1000 IU of Vitamin D_3 and/or 0,5 g of omega 3 fatty acid. Participants were instructed to take orally 2 study capsules daily. Adherence to the intervention was monitored at each in-person contact (3-montly

phone calls and clinical visits at 12, 24, and 36 months) by participant self-report. Further, we measured blood levels of 25(OH)D with gold standard LC-APPI-MS/MS methodology and of PUFA with gold standard LC-MS/MS methodology in all participants at baseline, 12, 24, and 36 months.

Statistical analyses of the effect of the intervention on overall health and multiple individual organ functions of the participants were performed. DO-HEALTH is the first randomized controlled trial which collected data for a high-enough vitamin D dose and a 25-hydroxyvitamin D threshold for optimal health and chronic disease prevention, and which can provide insight for the **correct dosage of vitamin D and achieved blood levels of 25(OH)D**. Previous studies suggest that life expectancy among people with vitamin D deficiency is lower compared to those with replete vitamin D levels, which could in part be explained by an increased risk of cardio-vascular disease (37), colo-rectal cancer (38) and fractures (39). Furthermore, the results of preliminary studies indicate that vitamin D – connecting to a specific receptor – has a direct, positive effect on muscle strength and function(40). For optimal translation of this benefit into fall prevention, it is essential that the dose of vitamin D is right, as excess doses may reverse the protective effect (41) (42). **Based on our study, we have, for the first time, an indication that there is a therapeutic range for achieved blood levels of vitamin D (25-Hydroxyvitamin D) with respect to several health outcomes: not too little, and not too much**.

DO-HEALTH is among the few studies which address the long-term use of omega-3-fatty acids, and its effects with regards to cardio-vascular health, bone health, muscle health, brain health, and immunity. Moreover, DO-HEALTH will provide data on the long-term effect of omega-3 fatty acids against placebo and combined with vitamin D and/or exercise.

A manuscript disclosing DO-HEALTH evidence will be published soon.

1.3.4 Evidence on the role of a well-defined exercise program as an animated instruction tool for the prevention of organ-specific function and chronic disease

DO-HEALTH participants were randomised either to the Exercise intervention (Strength exercise) program validated in the DO-HEALTH pilot trial(43), or to a Control exercise (Flexibility exercise) program, designed in DO-HEALTH to serve as a high-quality control and expected to have no benefit on the endpoints tested in DO-HEALTH. The exercises programs were supported by a one-time instruction at baseline plus a paper-based manual available in German, French, Portuguese and English, and a DVD, language free, with an animated instruction (avatar), both developed for DO-HEALTH.

Participants were instructed to perform the home exercise program for 30 minutes 3 times a week. Adherence to the exercise program (strength and flexibility) was monitored at each in-person contact (3-montly phone calls and clinical visits at 12, 24, and 36 months) by participant self-report and a blinded study nurse.

DO-HEALTH is the first randomized controlled trial which collected data on the effect of an unsupervised home exercise program on the 5 primary health domains of DO-HEALTH, plus its combined effect with vitamin D and / or omega-3 fatty acids. A manuscript disclosing DO-HEALTH evidence will be published soon.

1.3.5 Rigorous scientific evidence on 3 promising public health interventions for 5 relevant health endpoints supported by mechanistic evidence from biomarker studies and supported by long-term safety and comparative effectiveness data

In addition to studying clinical endpoints, DO-HEALTH extensively investigated a large set of biomarkers (organ-specific biomarkers, inflammation and immunity markers, bone and muscle markers, adherence markers) which support the clinical endpoints at the mechanistic level, and provide safety data with regard to the investigated interventions in adults age 70 and older. The biomarkers were measured at all timepoints and in all 2157 DO-HEALTH participants by DO-HEALTH partners laboratories.

The modulation effect of the three interventions, alone and in combination, on key biomarkers of bone and muscle health, as well as immunity was investigated.

With measurements of most common organ-specific biomarkers, DO-HEALTH also aims to identify mechanistic pathways that support the effect of the interventions on other primary and secondary health domains in DO-HEALTH.

Adherence to the study medication was assessed by measuring serum 25-hydroxyvitamin D and polyunsaturated fatty acids (PUFAs).

As an important stepping stone for future research on healthy ageing, the Centre on Aging and Mobility at the University of Zurich built up a biobank of more than 200,000 blood samples to identify novel risk profiles and novel treatments that support adults to stay healthy and active longer.

1.3.6 Assessment of a large range of biomarkers to establish reference ranges at older age (which do not exist today)

Current laboratory references of most biomarkers were established for middle-aged adults. Notably, however, biomarkers of virtually all organ functions are strongly influenced by age (44, 45). Thus, it is of concern that laboratory reference values of most organ functions refer to middle-aged adults and are missing for older adults. This concern is further enhanced by the fact that older adults carry the highest risk of chronic disease and hence undergo laboratory testing most frequently.

In DO-HEALTH, organ specific biomarkers of five primary health domains (cardio-vascular, bone, muscle, brain, and immunity) and several secondary health domains (i.e. glucose-metabolic, kidney, liver, global health) were measured in all participants at all time points, also to establish for the first-time reference intervals for a wide range of common biomarkers for older adults.

The intervals were inferred from the results of DO-HEALTH participants at baseline.

These reference ranges will be published shortly.

1.3.7 User-friendly, safe and direct touch screen-based data entry system

Data accuracy and safety were central to DO-HEALTH's success. To achieve this goal, DO-HEALTH developed a user-friendly, safe, and direct touch-screen based Electronic Data Capture (EDC) system for the electronic data capture of DO-HEALTH elaborate CRFs and questionnaires.

This versatile system, running on an iPad or any tablet, allows randomization, supply management, scheduling, trial monitoring, direct data entry of clinical assessments/questionnaires, edit checks, data storage and data extraction. The system was used at all recruitment sites, with speedy data check on site (reference ranges for correct data entry) and transfer to the centralized DO-HEALTH database. Data accuracy was established in several validation procedures in DO-HEALTH.

Importantly, the direct data entry software on tablet computers was used by all DO-HEALTH participants and very positive feed-back were given due to its simple touch screen and "one question per screen" concept. DO-HEALTH established that the DO-HEALTH EDC application can be used by adults without prior computer experience and makes long questionnaires entertaining. Vision for older adults is simplified as only one question is seen per tablet window.

1.3.8 Web-based teaching software to explain and implement DO-HEALTH findings for the 3 interventions

DO-HEALTH developed a simple interactive and visually appealing software tool for the broad public to learn what they can do individually to improve their health based on DO-HEALTH findings regarding the 5 primary health domains. The software explains the benefit of each single intervention individually and the benefit of combining two or all three interventions for all 5 primary health domains and individualized by gender and age.

The DO-HEALTH teaching software tool first shows the overall results of DO-HEALTH for the 5 primary health domains. Then, personalization by the user can take place. The user is invited to show the results for subgroups that more closely resemble himself: The user can select just a gender, or a combination of gender, age (70-<75 years, or 75 and older). When the user clicks the appropriate button, the results for the selected group are shown. The user can view the results, then choose another subgroup or return to the overall results.

To make it even easier to convey the information to the individual user, the tool provides a guided walk-through, with a first screen showing the table with the results for the group with no interventions, taking into account any personalization selected by the user. The user can then select an intervention to view and the results for that intervention are displayed. The user is invited to select a second intervention and the results and commentary for the group that took both the previous intervention and the additional intervention are shown. Finally, the user is invited to add the third intervention. The results of taking all three interventions are shown, along with a description of each result to guide the user. At this point the walk-through is complete. The user can choose another walk-through, either to change the order in which the interventions are added or to change the personalization.

1.3.9 DO-HEALTH health economic model

Based on a systematic literature search on cost-effectiveness analyses and decision-analytic models on the DO-HEALTH endpoints, only few potentially relevant articles were identified, with none of them including the multiple endpoints of the DO-HEALTH Study or examples for multi-outcome or multi-disease decision models (except one economic study explicitly evaluating two clinical outcomes, falls and fractures(46).

Consequently, the DO-HEALTH economic model is – to our knowledge – the first investigating multiple clinical outcomes and interventions. Further, the findings in the literature show mainly that the socioeconomic costs for fractures, falls or dementia are high and the interventions like vitamin D supplementation or exercise might be effective and cost effective.

We developed an economic model allowing for the evaluation of multiple outcomes which was applied for an economic evaluation of the DO-HEALTH interventions, as individual interventions, and in combination as a multi-modal intervention.

1.3.10 Extension of the FRAX fracture prediction model by the risk of falling

In a first step, the ten-year absolute fracture probability was assessed with the FRAX® tool (version 3.9) in DO-HEALTH participants blinded to any outcome variable (baseline data). The mean probability of a major fracture was 12% and, for a hip fracture was 4% when BMD was used in the FRAX model.

In a second step, falls, as observed and registered in DO-HEALTH, were evaluated as potential risk factors in the FRAX algorithm.

The results of the DO-HEALTH fall data enhancement of the FRAX-tool will be published shortly.

1.4. Potential impact, main dissemination activities and exploitation of results

1.4.1 Potential impact

DO-HEALTH is the largest ageing study to date designed to extend healthy life expectancy by delaying physiologic aging at multi-organ sites.

DO-HEALTH will contribute to better clinical management of the community-dwelling adult population age 70 and older:

- ✓ identifying individuals at risk developing specific chronic diseases (age-specific reference intervals of laboratory biomarkers and endpoints)
- ✓ identifying individuals at risk for low adherence to the 3 DO-HEALTH strategies and how to overcome barriers of low adherence in a personalized implementation plan supported by the DO-HEALTH implementation tools (DO-HEALTH educational web-based software tool, motivational exercise video)

- ✓ identifying inactive individuals (DO-HEALTH physical activity assessment) and individuals with specific nutrient deficiencies (DO-HEALTH assessment of dietary intake of protein and calcium intake and biomarkers for vitamin D, omega-3 fats, B-vitamins, and iron deficiencies), and implementing an extended intervention plan including the 3 DO-HEALTH strategies plus a correction of other nutritional deficiencies relevant to the optimal benefit of DO-HEALTH strategies
- ✓ implementing appropriate clinical interventions and risk assessments based on age-appropriate biomarker reference and threshold values of chronic diseases at older age (DO-HEALTH endpoints and biomarkers)

DO-HEALTH will assess the potential healthcare costs reduction: Currently there are no health economic evaluations published for omega-3 fatty acids or a well-defined home exercise program, or the combination of these interventions. Thus, obtaining trial-based evidence is critical to inform policy makers about the health economic impact.

Last, the DO-HEALTH – VITAL collaboration will enable the direct comparison of the effects of Vitamin D and omega-3 fats in Europe and in the US (pooled analysis), plus assess the impact of these nutrients on major health outcomes in adults age 50 years and older (VITAL) and the impact of these nutrients on 5 primary health domains (DO-HEALTH) that contribute to the incidence of major health events that lead to frailty.

For two of the three interventions tested in DO-HEALTH, vitamin D and omega-3 fats, the DO-HEALTH trial has been designed as a complementary trial to the VITAL study funded by the National Institutes of Health (NIH) in the US, which is testing vitamin D and omega-3 fats in the same treatment dose, but with a focus on major cardiovascular and cancer events in 20,000 US adults aged 50 years and older, followed over 5 years with yearly questionnaires. The DO-HEALTH exploitation plan foresees a collaboration (pre-planned standardized endpoint assessment) and comparison of the two trials to enhance their individual and joint impact for chronic disease prevention in older adults globally.

1.4.2 Main dissemination activities

To date, due to the confidentiality of DO-HEALTH findings, dissemination activities focused mainly on DO-HEALTH progress, and they were supported by DO-HEALTH dissemination partner IOF, with a link to the IOF website providing videos and news:

- ✓ https://www.iofbonehealth.org/do-health-multi-centre-clinical-trial-healthy-ageing-achieves-first-milestone (September 2013),
- ✓ https://www.iofbonehealth.org/news/do-health-annual-meeting-charts-progress (February 2014),
- ✓ https://www.iofbonehealth.org/news/do-health-track-meet-recruitment-targets-still-seeking-participants (July 2014),
- ✓ https://www.iofbonehealth.org/news/do-health-study-meets-recruitment-target-begins-baseline-assessment (March 2015),
- ✓ https://www.iofbonehealth.org/news/annual-do-health-meeting-reviews-progress-and-challenges (March 2016)

- ✓ https://www.iofbonehealth.org/news/latest-news-about-do-health-europes-largest-study-ageing (November 2017)

In addition, two International DO-HEALTH Symposia (ICFSR 2017 and WCO – IOF - ESCEO 2018) presented DO-HEALTH preliminary findings (NO disclosure of DO-HEALTH interventions results).

1.4.3 Exploitation of results

DO-HEALTH yields important scientific and public health breakthroughs, guiding the establishment of daily nutritional recommendations for vitamin D and omega-3 fats, of recommendations for e.g., better bone and muscle health at older age, of laboratory reference ranges for a large set of common laboratory markers which are missing today for community-dwelling adults age 70 and older, and of future preventive and therapeutic measures.

In addition, DO-HEALTH developed innovative tools which have a potential for exploitation, such as the practical tablet computer-based direct data entry system targeted at adults, the interactive software tool for adults and health professionals on how DO-HEALTH findings can be translated into personal use, the health economic computer model and the FRAX fall-extension (inclusion of fall in the WHO FRAX algorithm).

The coordinating centre (UZH) is currently collaborating with Unitectra, the joint technology transfer office of the Universities of Basel, Bern and Zurich, to evaluate DO-HEALTH Exploitation plan and the further steps to protect DO-HEALTH exploitable results. In this respect, DO-HEALTH findings must be temporarily kept confidential.

1.5. Address of the project public website and relevant contact details

Project website: www.do-health.eu

Project logo:

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References

1. United Nations, Department of Economic and Social Affairs, Population Division. World Population Ageing Report. New York: 2015.
2. European Economy. Special Report. No. 1. 2006. European Commission. Directorate-General for Economic and Financial Affairs., 2006 Contract No.: 1.2006.
3. Eberstadt N., H. G. Europe's coming demographic challenge: unlocking the value of health. American Enterprise Institute for Public Policy Research. 2007.
4. Recent demographic developments in Europe 2005. European population Committee of the Council of Europe, 2006.
5. Lanzieri G, Corsini V. First demographic estimates for 2005. Eurostat, 2006.
6. Lee RD. Global population aging and its economic consequences. Washington , DC:AEI Press, 2007. 2007.
7. Active Ageing: A Policy Framework. World Health Organization, 2002.
8. Jackson RD, Shidham S. The role of hormone therapy and calcium plus vitamin D for reduction of bone loss and risk for fractures: lessons learned from the Women's Health Initiative. Curr Osteoporos Rep. 2007;5(4):153-9.
9. European Parliament Hearing. Vitamin D nutritional policy in Europe : The need for prevention, education & consumer choice. Brussels, Belgium2010.
10. Jorde R, Grimnes G. Vitamin D and health: The need for more randomized controlled trials. The Journal of Steroid Biochemistry and Molecular Biology. 2015;148:269-74.
11. Grossman DC, Curry SJ, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al. Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults: US Preventive Services Task Force Recommendation Statement. Jama. 2018;319(15):1592-9.
12. Bischoff-Ferrari HA, Can U, Staehelin HB, Platz A, Henschkowski J, Michel BA, et al. Severe vitamin D deficiency in Swiss hip fracture patients. Bone. 2008;42(3):597-602.
13. Burnand B, Sloutskis D, Gianoli F, Cornuz J, Rickenbach M, Paccaud F, et al. Serum 25-hydroxyvitamin D: distribution and determinants in the Swiss population. Am J Clin Nutr. 1992;56(3):537-42.
14. van der Wielen RP, Lowik MR, van den Berg H, de Groot LC, Haller J, Moreiras O, et al. Serum vitamin D concentrations among elderly people in Europe. Lancet (London, England). 1995;346(8969):207-10.
15. Santos A, Amaral TF, Guerra RS, Sousa AS, Álvares L, Moreira P, et al. Vitamin D status and associated factors among Portuguese older adults: results from the Nutrition UP 65 cross-sectional study. BMJ Open. 2017;7(6).
16. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? The Journal of Steroid Biochemistry and Molecular Biology. 2014;144:138-45.
17. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, Hathcock J, Giovannucci E, Willett WC. Benefit-risk assessment of vitamin D supplementation. Osteoporos Int. 2010;21(7):1121-32.
18. Goodwill AM, Szoeke C. A Systematic Review and Meta-Analysis of The Effect of Low Vitamin D on Cognition. Journal of the American Geriatrics Society. 2017;65(10):2161-8.
19. Schottker B, Jorde R, Peasey A, Thorand B, Jansen EH, Groot L, et al. Vitamin D and mortality: meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the United States. BMJ (Clinical research ed). 2014;348:g3656.
20. Sommer I, Griebler U, Kien C, Auer S, Klerings I, Hammer R, et al. Vitamin D deficiency as a risk factor for dementia: a systematic review and meta-analysis. BMC geriatrics. 2017;17(1):16.
21. Tylavsky FA, Ryder KM, Li R, Park V, Womack C, Norwood J, et al. Preliminary findings: 25(OH)D levels and PTH are indicators of rapid bone accrual in pubertal children. J Am Coll Nutr. 2007;26(5):462-70.
22. Dattani JT, Exton-Smith AN, Stephen JM. Vitamin D status of the elderly in relation to age and exposure to sunlight. Hum Nutr Clin Nutr. 1984;38(2):131-7.
23. Holick MF. Environmental factors that influence the cutaneous production of vitamin D. Am J Clin Nutr. 1995;61(3 Suppl):638S-45S.

24. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Washington (DC): National Academies Press (US); 2011.
25. 2010 AGS / BGS Clinical Practice Guideline: Prevention of Falls in Older Persons. American Geriatrics Society, 2010.
26. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int. 2010;21(7):1151-4.
27. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin d deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911-30.
28. Michael YL, Whitlock EP, Lin JS, Fu R, O'Connor EA, Gold R. Primary care-relevant interventions to prevent falling in older adults: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med. 2010;153(12):815-25.
29. van der Zwaluw NL, van de Rest O, Tieland M, Adam JJ, Hiddink GJ, van Loon LJ, et al. The impact of protein supplementation on cognitive performance in frail elderly. European journal of nutrition. 2014;53(3):803-12.
30. Ian Givens D, Gibbs RA. Current intakes of EPA and DHA in European populations and the potential of animal-derived foods to increase them. Proc Nutr Soc. 2008;67(3):273-80.
31. Bugeja G, Kumar A, Banerjee AK. Exclusion of elderly people from clinical research: a descriptive study of published reports. BMJ (Clinical research ed). 1997;315(7115):1059.
32. Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. Jama. 1992;268(11):1417-22.
33. Peat G, Birrell F, Cumming J, Doherty M, Simpson H, Conaghan PG. Under-representation of the elderly in osteoarthritis clinical trials. Rheumatology (Oxford). 2010.
34. Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol. 2003;21(7):1383-9.
35. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. Jama. 2004;291(22):2720-6.
36. Cummings SR, Nevitt MC, Kidd S. Forgetting falls. The limited accuracy of recall of falls in the elderly. Journal of the American Geriatrics Society. 1988;36(7):613-6.
37. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008;117(4):503-11.
38. Lee JE, Li H, Chan AT, Hollis BW, Lee IM, Stampfer MJ, et al. Circulating levels of vitamin D and colon and rectal cancer: the Physicians' Health Study and a meta-analysis of prospective studies. Cancer prevention research (Philadelphia, Pa). 2011;4(5):735-43.
39. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr. 2006;84(1):18-28.
40. Ceglia L, Niramitmahapanya S, da Silva Morais M, Rivas DA, Harris SS, Bischoff-Ferrari H, et al. A randomized study on the effect of vitamin D(3) supplementation on skeletal muscle morphology and vitamin D receptor concentration in older women. J Clin Endocrinol Metab. 2013;98(12):E1927-35.
41. Smith LM, Gallagher JC, Suiter C. Medium doses of daily vitamin D decrease falls and higher doses of daily vitamin D3 increase falls: A randomized clinical trial. J Steroid Biochem Mol Biol. 2017;173:317-22.
42. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, et al. Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline: A Randomized Clinical Trial. JAMA internal medicine. 2016;176(2):175-83.
43. Bischoff-Ferrari HA D-HB, Platz A, Orav EJ, Stahelin HB, Willett WC, et al. . Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture: a randomized controlled trial. . Archives of internal medicine. 2010;170((9)):813-20.
44. Engelfriet PM, Jansen EH, Picavet HS, Dolle ME. Biochemical markers of aging for longitudinal studies in humans. Epidemiologic reviews. 2013;35:132-51.

45. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. The journals of gerontology Series A, Biological sciences and medical sciences. 2014;69 Suppl 1:S4-9.
46. Patil R, et al. Cost-effectiveness of vitamin D supplementation and exercise in preventing injurious falls among older home-dwelling women: findings from an RCT. . Osteoporos Int. 2016; 27((1)):193-201.