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Uit projectplan (svp zoveel mogelijk invullen)

1. Projectinformatie

1.1 Organisatie/financiering *(keuze maken)*	TKI A&F
1.2 Projectnummer	AF-15502
1.3 Project titel	Mitochondrial Health
1.4 Projectleider *(naam en emailadres)*	Prof. dr. P. Schrauwen p.schrauwen@maastrichtuniversity.nl
1.5 Startdatum (*dd-mm-jjjj)*	1 juli 2016
1.6 Einddatum (*dd-mm-jjjj)*	31 december 2020
1.7 MMIP primair *(nummer en naam van het MMIP, zie overzicht bijlage 1)*	D2 Gezonde voeding een makkelijke keuze. Deelprogramma: relatie voeding en gezondheid gericht op gezond opgroeien en ouder worden.
1.8 MMIP secundair *(deze alleen invullen als er een 2e MMIP is waar het project aan bijdraagt)*	

2. Projectomschrijving

2.1 Samenvatting).

Mitochondria, the cell's powerhouses, are essential organelles in all cells relying on aerobic metabolism to maintain cellular energy levels necessary for all vital processes in the cell and human body. It has been known for decades that aging is associated with a decline in mitochondrial function of the skeletal muscle, and it is known that with aging muscle function also declines. Despite this fact, it is only recently that the therapeutic importance of mitochondria has become fully appreciated. Improving mitochondrial activity can not only potentially delay the general aging process, but more importantly also retard the onset of diseases linked with aging, such as loss of muscle mass and physical function. This not only has led to an intense interest to identify molecular pathways that govern mitochondrial number and function, but also spurred an intense search to identify new nutrients and drugs that can be used to improve mitochondrial function. Relevant to TI Food and Nutrition, mitochondria are very sensitive to nutritional signals, which is not surprising given the role of these organelles in nutrient handling. This opens the way to explore the potential of food components and specific nutrients to boost muscle mitochondrial function, especially in the elderly. As such, the project aims to find new nutritional means to improve muscle health and help in the prevention and improvement of age-related disturbances.

2.2 Doel van het project

Healthy nutrition plays an important role in maintaining health, and can also help to prevent the onset of loss of physical function and health that is associated with aging. The project Mitochondrial Health within TIFN focused on evaluating novel food components on mitochondrial metabolism and its relation to muscle health, one of the main tissues affected by aging. It is expected that basic science in *in vitro* muscle cell models can reveal novel food

components that affect mitochondrial metabolism, and can unravel the underlying mechanisms.

Using short-term human intervention studies, the translational aspect of the potential of such food components to boost mitochondrial function is tested in the elderly population, with a focus on those with compromised physical function. Cross-sectional studies were used to investigate the relationship between muscle mitochondrial function and muscle health in elderly, whereas we used large cohort studies to investigate the relationship between habitual food consumption and markers of muscle health and physical function. Finally, we aimed to develop tools and identify novel biomarkers of mitochondrial function that can be applied in observational and intervention studies.

It is anticipated that the project Mitochondrial Health will provide the industrial partners with novel methods and insights in the potential of food components and specific nutrients to prevent, delay or improve aging associated decline and disturbances in muscle health and physical function, by targeting mitochondrial function.

2.3 Motivatie

Due to the improved health care system in many countries, people are getting older and older. However, with advancing age, also comes a decline in physical function and an increased risk of chronic diseases. Healthy nutrition is recognized as an important pilar in the prevention of such age-related declines in physical function and health. In that context, mitochondria play a central role as these organelles are central in the combustion of our nutritients to yield energy. With aging, the function of mitochondria declines. Due to the pivotal role of mitochondria in nutrient combustion, their function is also under the biological regulation of nutritional sensors. More knowledge on this, and how food and diet could boost mitochondrial function can therefore have major impact on the function of mitochondria with age, and thereby help to prevent age-related decline in health.

2.4 Resultaat

The TIFN project MitoHealth is divided in four workpackages, covering the wide range of fundamental, basic science to human (cohort) studies. Results will be described below per workpackage.

WP1: Although it is known that both mitochondrial function and muscle health declines with age, the exact interrelation has not been shown. In WP1, a cross-sectional human study was performed in which mitochondrial function and a large range of muscle function parameters was determined in young (20-30 years), healthy volunteers as well as in three groups of older (65-80 years) participant: endurance trained, normal physical active and pre-frail volunteers. In addition, from muscle biopsies taken from those volunteers, human primary myotubes were cultured for *in vitro* studies and extensive metabolic characterization of cells derived from young vs. elderly donors using fluxomics and also mitochondrial function using seahorse analysis. Regarding the cell work, no difference was found in phenotype between the old and the young donors. Furthermore, these muscle cells have been subjected to proprionylation while studying its subsequent effects on mitochondrial function (WP1 – WP2 collaboration).

The cross-sectional study revealed that older adults displayed a lower *in vivo* and *ex vivo* mitochondrial capacity, maximal aerobic capacity, exercise efficiency, muscle strength, insulin sensitivity, gait stability following a perturbation, and walking performance when compared to young adults, despite similar habitual physical activity levels and comparable levels of muscle volume. In comparison to older adults with normal physical activity levels, endurance-trained older adults had a higher *ex vivo* mitochondrial function, maximal aerobic capacity, exercise efficiency, muscle strength and insulin sensitivity ($p = 0.023$). Measures for muscle health and mitochondrial capacity in physically impaired older individuals were not different from older adults with normal physical activity levels. In the entire cohort, mitochondrial function was associated with muscle strength, maximal aerobic capacity, exercise efficiency, and insulin sensitivity. Therefore, we conclude that aging is associated with a decline in mitochondrial capacity, exercise capacity and efficiency, gait stability, muscle function, and insulin sensitivity, even when maintaining an adequate daily physical activity level. Nevertheless, a further increase in physical activity level, achieved through regular exercise training, can partially negate effects of aging. Finally, the observed correlations between mitochondrial capacity and muscle strength, exercise efficiency, and insulin sensitivity, support a link between mitochondrial function and age-associated deterioration of skeletal muscle.

The work of WP1 resulted in a thesis for candidate Lotte Grevendonk, which is to be defended mid 2021.

WP2:In the second workpackage, a novel, non-invasive method (Near-InfraRed Spectroscopy (NIRS)) was established to determine in vivo mitochondrial function. We demonstrated that NIRS was able to detect differences in mitochondrial capacity in the gastrocnemius muscle in a homogenous population of high- and low-fitness males and females, with a smaller expected difference in mitochondrial capacity than was previously assessed. Furthermore, we show that NIRS correlates with other measures of oxidative capacity, underlining the physiological relevance of NIRS assessment of mitochondrial capacity. This demonstrates that NIRS could be a valuable tool to study muscle mitochondrial capacity in an ageing population.

We next used NIRS to assess the effect of age on mitochondrial capacity in a population of older (65-71 years) and young (19-25 years) males. We showed that NIRS was able to detect differences in mitochondrial capacity between the two age groups in the gastrocnemius and vastus lateralis, but not tibialis anterior. This showed that not all muscle groups display similar mitochondrial ageing and, because we observed these effects despite similar physical activity, the lower mitochondrial capacity is likely a direct effect of ageing and cannot be completely prevented by physical activity. Nevertheless, a higher mitochondrial capacity was correlated with spending more time in moderate-to-vigorous physical activity, suggesting that physical activity might ameliorate part of the age-related decline in mitochondrial capacity.

We also used transcriptome sequencing to identify molecular mechanisms of ageing in vastus lateralis muscle biopsies in the aforementioned population. The significant regulated processes in older compared to young muscle included: cell-adhesion, the matrisome, innervation and inflammation, which were largely upregulated, and oxidative metabolism, which was downregulated. In accordance with the transcriptome results, the protein expression of some mitochondrial respiratory complexes was lower in older compared to young muscle. Moreover, the expression of these complexes in the older group was correlated

with in vivo mitochondrial capacity in the vastus lateralis. This showed that the observed lower mitochondrial capacity could be explained by a lower expression of mitochondrial complex proteins and further substantiated the use of NIRS to measure mitochondrial capacity in vivo.

Furthermore, we performed cell culture studies in WP2 and focused on protein propionylation. We showed that increasing propionylation by exposure to pathophysiological concentrations of propionate induced impaired mitochondrial function in cultured fibroblasts and liver cells. Yet, this effect was not observed in cultured muscle cells, possibly due to differences in metabolic handling of propionyl-CoA. We also showed that exposure to propionate impairs skeletal muscle differentiation.

The work of WP2 resulted in a thesis for candidate Bart Lagerwaard, which is to be defended in March, 2021.

WP3: In the third workpackage, we investigated how nutrient and diet could potentially affect mitochondrial function and metabolic health in older people. To this end, we turned our attention to Nicotinamide dinucleotide metabolism. Thus, nicotinamide dinucleotide (NAD^+) supplementation has been proposed as a potential modality capable of promoting healthy aging and negating age-dependent decline of skeletal muscle mass and function. To investigate the efficacy of NAD^+-precursor supplementation with L-tryptophan, nicotinic acid, and nicotinamide on skeletal muscle mitochondrial function, we conducted a randomized, double-blind, controlled trial in fourteen community-dwelling, older adults with impaired physical function. We supplemented with 207.5 mg of niacin equivalents for 32 days, therein resembling an increased dietary intake. We found that following supplementation, skeletal muscle NAD^+ concentrations were not significantly different compared to the control condition, whereas skeletal muscle methyl-nicotinamide (MeNAM) levels were significantly higher under NAD^+-precursor supplementation, suggesting increased NAD^+ metabolism. We next performed a large range of measurements to metabolically phenotype the effect of NAD supplementation. We found that *ex vivo* mitochondrial respiration capacity did not improve under NAD^+-precursor supplementation, neither did net exercise efficiency as measured during a submaximal cycling test. We also found no effect of NAD supplementation on skeletal muscle acylcarnitine levels. Also, body composition was unaffected by the supplementation, as well were the levels of hepatic fat content and muscle volume not affected by NAD. We also determined basal energy expenditure and substrate oxidation rates using indirect calorimetry, but again these were unaffected by NAD supplementation. Measures of physical function, such as SPBB were also not affected by NAD supplementation.

Since the start of the MitoHealth project, other human experimental studies have been published, applying NAD supplementation in people with obesity and type 2 diabetes. Overall, our findings are consistent with these previous findings on NAD^+ efficacy in humans and we show in community-dwelling, older adults with impaired physical function that NAD^+-precursor supplementation through L-tryptophan, nicotinic acid, and nicotinamide does not improve mitochondrial or skeletal muscle function. As one explanation, it may be suggested that starting levels of NAD in our volunteers may have been too high and that NAD supplementation only works in those volunteers that have a deficit in NAD concentrations.

The second aim of this workpackage was to investigate the impact of another dietary approach on mitochondrial function. Here, we aimed to investigate the effect of a combination of fish oil and complex lipids on outcome parameters as measured in the NAD supplementation study. Unfortunately, due to COVID-19 this experiment had to be preliminary terminated and was unable to be finalized.

The work of WP3 resulted in a thesis for candidate Niels Connell, which was defended on January 22, 2021.

WP4: the aim of workpackage 4 was to investigate the relationship between food intake, markers of mitochondrial function and muscle health. Identification of novel biomarkers for mitochondrial function was part of WP4 too.

Observational data from the Nu-Age study (1250 older adults across Europe) were analysed, to evaluate how habitual food intake, i.e. the intake of B-vitamins (3, 6, 12 and folate), and plasma homocysteine and urinary biomarkers of niacin status (n=252) relate to measures of muscle health and physical function in an elderly population. Intake of vitamin B-6 was related to lower chair rise test time. Vitamin B6 intake was also significantly associated with handgrip strength, but for this association, a significant interaction effect between vitamin B-6intake and physical activity level was found. In participants with the lowest level of physical activity,higher intake of vitamin B6 tended to be associated with greater hand grip strength, while in participants in the highest quartile of physical activity higher intake was associated with lower handgrip strength. No evidence was found for an association between intake of niacin, vitamin B-12 or folate and physical performance, or for mediation by niacin status or homocysteine concentrations. Vitamin B-6 might be of added value in preventing age-related decline in physical performance, especially in cases where increasing physical activity is not feasible.

In a prospective cohort of renal transplant recipients and healthy kidney donors biomarkers of niacin nutritional status were investigated. While the World Health Organisation WHO) recommends urinary excretion of N1-Mehylnicotinamide and/or the urinary ratio of N1-Methylnicotinamide and its metabolite N1-Methyl-2-Pyridone-5-Carboxamide as biomarker(s) of niacin status, we found that both markers are strongly influenced by mild degrees of renal dysfunction, while the sum of N1-Methylnicotinamide and N1-Methyl-2-Pyridone-5-Carboxamide is not dependent on renal dysfunction and serves as a much more accurate marker of niacin status in any circumstance. Because renal dysfunction is very common in elderly people and other populations at high risk of poor niacin status, this finding has important implications for the general population and for future recommendations of the WHO on biomarkers for niacin status. We also found that low niacin status is very common in renal transplant recipients and that such a low status is in important risk factor for premature mortality in this population, holding a strong plea for further studies on niacin supplementation in this population and for prospective studies on the association of niacin status with premature mortality in elderly people and other high risk populations.

The work of WP4 resulted in a thesis for candidate Pol Grootswagers, which was defended on 11 november, 2020. A second thesis for candidate Carolien Deen is expected in 2021.

Jaarrapportage (svp ook laatste jaar invullen)

3. Status project

3.1 Status project *(keuze maken)*	project has been finalized
3.2 Toelichting incl. voorziene wijzigingen t.o.v. het oorspronkelijke werkplan	As planned, the project was to be finalized in September 2020. Due to COVID-19, some delay in finalizing the last experiments occurred and the final end date was set at 31 december 2020. Most activities could be finalized according to planning. Only in WP3, a second human nutritional intervention, which was planned for – and started in 2020, had to be preliminary halted. Finally it was decided to terminate this study.

4. Behaalde resultaten

4.1 Korte beschrijving van de inhoudelijke resultaten en hun bijdrage aan het MMIP (zoals beschreven in 2.2)

The MitoHealth project revealed that mitochondrial function in skeletal muscle declines with age and can be restored by physical activity levels. More important, mitochondrial function in skeletal muscle is related to markers and measures of muscle health and physical functioning. These findings indicate that mitochondria are an important target for intervention to improve and maintain muscle health with aging. We have investigated if NAD metabolism could be such a way to improve mitochondrial function, but the results revealed that boosting NAD metabolism did not alter mitochondrial function. From cross sectional data, vitamin B6 was identified as a potential target to improve muscle health.
Unfortunately, the project was too short and interrupted by COVID-19 to make firm conclusions on how food and nutrition could help to increase mitochondrial function, but the MitoHealth project showed clear indications that mitochondria should be considered as a target for healthy aging. In that respect, the interaction between exercise/physical activity and food and nutrition may also be of interest.

4.2 Deliverables (bijeenkomsten en andere output, die niet benoemd wordt in 4.3 en 4.4)

A midterm review with international reviewers was held. In addition, an end symposium was held in December 2020 for the industrial partners, where the main results of the project were presented and discussed.

4.3 Communicatie (lijsten)

4.3.1 Wetenschappelijke artikelen en hun doi (*Digital Object Identifiers)*

Lagerwaard B, Keijer J, McCully KK, de Boer VCJ, Nieuwenhuizen AG. In vivo assessment of muscle mitochondrial function in healthy, young males in relation to parameters of aerobic fitness. Eur J Appl Physiol. 2019 Aug;119(8):1799-1808. doi: 10.1007/s00421-019-04169-8. Epub 2019 Jun 8. PMID: 31177324; PMCID: PMC6647177.

Deen CPJ, van der Veen A, van Faassen M, Minović I, Gomes-Neto AW, Geleijnse JM, Borgonjen-van den Berg KJ, Kema IP, Bakker SJL. Urinary Excretion of N1-Methylnicotinamide, as a Biomarker of Niacin Status, and Mortality in Renal Transplant Recipients. J Clin Med. 2019 Nov 12;8(11):1948. doi: 10.3390/jcm8111948. PMID: 31726722; PMCID: PMC6912198.

Lagerwaard B, Nieuwenhuizen AG, de Boer VCJ, Keijer J. In vivo assessment of mitochondrial capacity using NIRS in locomotor muscles of young and elderly males with similar physical activity levels. Geroscience. 2020 Feb;42(1):299-310. doi: 10.1007/s11357-019-00145-4. Epub 2019 Dec 19. PMID: 31858399; PMCID: PMC7031190.

Deen CPJ, van der Veen A, Gomes-Neto AW, Geleijnse JM, Borgonjen-van den Berg KJ, Heiner-Fokkema MR, Kema IP, Bakker SJL. Urinary Excretion of N1-methyl-2-pyridone-5-carboxamide and N1-methylnicotinamide in Renal Transplant Recipients and Donors. J Clin Med. 2020 Feb 6;9(2):437. doi: 10.3390/jcm9020437. PMID: 32041099; PMCID: PMC7074074.

Veen AV, Minović I, Faassen MV, Gomes-Neto AW, Berger SP, Bakker SJL, Kema IP. Urinary Excretion of 6-Sulfatoxymelatonin, the Main Metabolite of Melatonin, and Mortality in Stable Outpatient Renal Transplant Recipients. J Clin Med. 2020 Feb 14;9(2):525. doi: 10.3390/jcm9020525. PMID: 32075158; PMCID: PMC7073605.

Deen CPJ, Veen AV, Gomes-Neto AW, Geleijnse JM, Berg KJBD, Heiner-Fokkema MR, Kema IP, Bakker SJL. Urinary Excretion of N1-Methylnicotinamide and N1-Methyl-2-Pyridone-5-Carboxamide and Mortality in Kidney Transplant Recipients. Nutrients. 2020 Jul 10;12(7):2059. doi: 10.3390/nu12072059. PMID: 32664445; PMCID: PMC7400946.

Grootwagers P. Nutritional strategies to improve muscle quality during aging. PhD thesis, Wageningen University, Wageningen, the Netherlands. 2020 Nov 11. doi: 10.18174/530397.

4.3.2 Rapporten/artikelen in vakbladen

n.a.

4.3.3 Overige communicatie-uitingen (inleidingen/posters/radio-tv/social media/workshops/beurzen)

Lagerwaard B, Pougovkina O, Te Brinke H, Wanders RJA, Nieuwenhuizen AG, Keijer J, De Boer VCJ. Protein hyperpropionylation contributes to mitochondrial dysfunction and impairs C2C12 myoblast differentiation. Poster presentation at Mitochondrial Physiology Summer School, Copenhagen, 21 August 2017

Lagerwaard B, De Boer V, Nieuwenhuizen A, Keijer J. Using near-infrared spectroscopy to measure mitochondrial function. Lecture during course Energy metabolism and body composition, Wageningen, the Netherlands, 5 March 2018.

Bart Lagerwaard, Vincent C.J. de Boer, Arie G. Nieuwenhuizen, Kevin K. McCully, Jaap Keijer. Novel method for non-invasive assessment of muscle mitochondrial function in healthy, young males and its relation to parameters of aerobic fitness. Oral presentation during NUGOweek, Newcastle, United Kingdom, 5 September 2018.

Grootswagers P. Maintaining mitochondrial health during ageing: The role of B-vitamins. Oral presentation during Dutch Nutritional Science Days, Heeze, The Netherlands, 11 October 2018.

Bart Lagerwaard, Vincent C.J. de Boer, Arie G. Nieuwenhuizen, Kevin K. McCully, Jaap Keijer. Novel method for non-invasive assessment of muscle mitochondrial function in healthy, young males and its relation to parameters of aerobic fitness. Oral presentation during Mitoscience, Amsterdam, The Netherlands, November 2018.

Schrauwen P. Mitochondrial dysfunction in skeletal muscle and type 2 diabetes. Invited keynote speaker during Keystone Symposium on Mitochondrial Biology in Heart and Skeletal Muscle/ Mitochondria in Aging and Age-Related Disease, Keystone, Colorado, USA, 13 January 2019.

Connell N. Mitochondria and muscle health in elderly. Oral presentation during Lille-Maastricht-Düsseldorf meeting, Lille, France, 4 July 2019.

Lagerwaard B, Pougovkina O, Te Brinke H, Wanders RJA, Nieuwenhuizen AG, Keijer J, De Boer VCJ. Protein hyperpropionylation impairs mitochondrial function and muscle cell differentiation. Abstract, oral presentation and poster during FASEB: The reversible protein acetylation in health and disease conference, 4 August 2019.

Lagerwaard B, Nieuwenhuizen AG, De Boer VCJ, Keijer J. In vivo assessment of muscle mitochondrial function in ageing research using near-infrared spectroscopy. Abstract and poster during TiFN retreat, 11 September 2019.

Grootswagers P, Deen CPJ, Berendsen AAM, Kema IP, Bakker SJL, de Groot LCPMG, Mensink M. Dietary intake of vitamin B3, B6, B12, folate in relation to physical functioning in healthy older European adults. Abstract and poster during TiFN retreat, 11 September 2019.

Grevendonk L, Fealy CE,Connell NJ, Hoeks J, Schrauwen P. Cross-sectional analysis of mitochondrial function and muscle health in elderly. Abstract and poster during TiFN retreat, 11 September 2019.

Schrauwen P. Skeletal muscle insulin resistance: role of mitochondria. Invited lecture during 55th annual meeting of the European Association for the Study of Diabetes (EASD), Barcelona, Spain, 16 September 2019.

Grevendonk L. Mitochondria and muscle health in elderly. Oral presentation during Nutrim symposium, Maastricht, The Netherlands, 27 November 2019.

4.4 Overige resultaten: technieken, apparaten, methodes

A novel, non-invasive method (Near-InfraRed Spectroscopy (NIRS)) was established to determine in vivo mitochondrial function. We demonstrated that NIRS was able to detect

differences in mitochondrial capacity in the gastrocnemius muscle in a homogenous population of high- and low-fitness males and females, with a smaller expected difference in mitochondrial capacity than was previously assessed. Furthermore, we show that NIRS correlates with other measures of oxidative capacity, underlining the physiological relevance of NIRS assessment of mitochondrial capacity. This demonstrates that NIRS could be a valuable tool to study muscle mitochondrial capacity in an ageing population. In a prospective cohort of renal transplant recipients and healthy kidney donors biomarkers of niacin nutritional status were investigated. It was found that urinary excretion of N1-methylnicotinamide can be used as a biomarker of niacin status, and mortality in renal transplant recipients.
4.5 Projectwebsite: geef het adres van de projectwebsite (indien beschikbaar)
https://www.tifn.nl/mitochondrial-health/

Eindrapportage

5. TRL bij afsluiting van een project

Technology Readiness Level (TRL) van de technologie bij afsluiting van het project. Er zijn twee indicatoren die verschillen in detailniveau. Vul zo mogelijk het detailniveau in. Als dat niet mogelijk is, vul dan de hoofdcategorie in.

5.1 Hoofdcategorie *(keuze maken)*	Fundamental research (TRL 1-3)
5.2 Detailcategorie bij start van het project *(in cijfers, nummer van de betreffende categorie, zie bijlage voor toelichting)*	TRL1 to TRL3
5.3 Detailcategorie bij afsluiting van het project	TRL4 to TRL5

6 Status project bij afronding

Status project *(keuze maken)*	2. Het project is naar tevredenheid afgerond, maar de inhoud van de mijlpalen is gewijzigd.

7 Output over het hele project

		aantal
7.1	**Aantal gerealiseerde wetenschappelijke publicaties** *gepubliceerde artikelen in peer-reviewed journals*	6
7.1 lijst	Zie lijst onder 4.3.1 voeg evt. artikelen uit eerdere jaren toe (incl. doi)	
7.2	**Aantal verwachte wetenschappelijke publicaties** *publicaties waarvan verwacht wordt dat ze gepubliceerd zullen worden in een peer-reviewed journal*	7

7.2 lijst	Janssens GE, Molenaars M, Herzorg K, Grevendonk L, Remie CME, ..., Pras-Raves ML, Luyf AC, Florquin S, van Weeghel M, van Kampen AHC, Moerland PD, Hoeks J, Schrauwen P, Vaz FM, Houtkooper RH. Bis(Monoacylglycero)-Phosphate (BMP) and its synthesis prevent longevity. Nature. Publication pending. Lagerwaard B, Bunschoten A, Nieuwenhuizen AG, de Boer VCJ, Keijer J. Changes in matrisome, synaptogenesis and mitochondrial gene expression as early muscle ageing signature in older compared to young males with similar physical activity levels. Publication pending. Grevendonk L, Connell NJ, McCrum C, Fealy C, Bilet L, Bruls YMH, Schrauwen-Hinderling VB, Jörgensen JA, Kornips-Moonen E, Schaar G, Havekes B, de Vogel J, Bragt-van Wijngaarden MCE, Meijer K, Hoeks J. Impact of aging and exercise on skeletal muscle mitochondrial capacity, energy metabolism and physical function: a cross-sectional study. Publication pending. Lagerwaard B, Janssen J, Cuijpers IC, Jaap Keijer1, De Boer VCJ, Nieuwenhuizen AG. Muscle mitochondrial capacity in high and low fitness females using near-infrared spectroscopy. Publication pending. Connel NJ, Grevendonk L, Fealy CE, Kornips-Moonen E, Bruls YMH, Schrauwen-Hinderling VB, de Vogel J, Zapata-Perez R, Houtkooper RH, Havekes B, Hoeks J, Schrauwen P. NAD+-precursor supplementation with L-tryptophan, nicotinic acid, and nicotinamide does not improve mitochondrial function and skeletal muscle function in physically compromised older adults. Publication pending Lagerwaard B, Hoeks J, Grevendonk L, Nieuwenhuizen AG, Keijer J, de Boer VCJ. Propionate hampers differentiation and modifies histone propionylation and acetylation in skeletal muscle cells. Publication pending. Grootswagers P, Mensink M, Berendsen AAM, Deen CPJ, Kema IP, Bakker SJL, Santoro A, Franceschi C, Meunier N, Malpuech-Brugère C, Bialecka-Debek A, Rolf K, Fairweather-Tait S, Jennings A, Feskens EJM, de Groot LCPGM. Vitamin B-6 intake is related to physical performance in European older adults - the NU-AGE study. Publication is pending.	
7.3	**Aantal gerealiseerde niet-wetenschappelijke publicaties** *rapporten, vakbladartikelen*	n.a.
7.3 lijst	Zie lijst onder 4.3.2 voeg evt. publicaties uit eerdere jaren toe	
7.4	**Aantal aangevraagde patenten** *Het aantal patenten die op basis van onderzoek uit het project zijn aangevraagd*	n.a.

7.4 lijst	Geef van elk patent de doi, wanneer beschikbaar	
7.5	**Aantal verleende licenties** *Het aantal verleende licenties die op basis van onderzoek uit het project zijn verleend*	n.a.
7.5 lijst		
7.6	**Aantal prototypes** *Het aantal gerealiseerde prototypes die op basis van onderzoek uit het project zijn ontwikkeld*	n.a.
7.6 lijst		
7.7	**Aantal demonstrators** *Het aantal gerealiseerde demonstrators die op basis van onderzoek uit het project zijn ontwikkeld*	n.a.
7.7 lijst		
7.8	**Aantal spin-offs/ spin-outs** *Het aantal spin-offs en spin-outs die op basis van onderzoek uit het project zijn voortgekomen.*	n.a.
7.8 lijst		
7.9	**Aantal nieuwe of verbeterde producten/ processen/diensten geïntroduceerd** *Het aantal producten dat verbeterd of nieuw ontwikkeld is/wordt en het aantal processen en diensten die verbeterd of nieuw is op basis van onderzoek uit het project.*	2
7.9 lijst	A novel, non-invasive method (Near-InfraRed Spectroscopy (NIRS)) was established to determine in vivo mitochondrial function. We demonstrated that NIRS was able to detect differences in mitochondrial capacity in the gastrocnemius muscle in a homogenous population of high- and low-fitness males and females, with a smaller expected difference in mitochondrial capacity than was previously assessed. Furthermore, we show that NIRS correlates with other measures of oxidative capacity, underlining the physiological relevance of NIRS assessment of mitochondrial capacity. This demonstrates that NIRS could be a valuable tool to study muscle mitochondrial capacity in an ageing population. The World Health Organisation WHO) currently recommends urinary excretion of N1-Mehylnicotinamide and/or the urinary ratio of N1-Methylnicotinamide and its metabolite N1-Methyl-2-Pyridone-5-Carboxamide as biomarker(s) of niacin status. Using the models of life kidney donation and renal transplantation, we found that both markers are invalid in circumstances of mild degrees of renal dysfunction, while the sum of N1-Methylnicotinamide and N1-Methyl-2-Pyridone-5-Carboxamide is a much more accurate marker of niacin status. Because mild degrees of renal dysfunction are very common in elderly people and other populations at high risk of poor niacin status, this finding has important implications for future recommendations by the WHO on the use of biomarkers for niacin status. We also found that low niacin status is very common in renal transplant recipients and that such a low status is in important risk factor for premature	

	mortality in this population. Niacin supplementation or advices for increasing niacin intake could therefore be very important for improving outcomes in this population, and the findings hold a strong plea for further prospective studies on niacin status and premature mortality in elderly people and other high risk populations.	

8 Impact

Impact betreft het verhaal van het project: een kwalitatieve omschrijving van hoe het project heeft bijgedragen aan de missies en/of het realiseren van economische kansen. Geef aan wat er met de ontwikkelde kennis/tools uit het project wordt gedaan. Geef een toelichting op de (bredere) bijdrage van het project aan de maatschappelijke uitdaging, zoals verwoord in 1.4b. De genoemde impact kan bijvoorbeeld betrekking hebben op:

- Producten, concepten, kennis e.d. die door de partners in de praktijk worden toegepast (nu of op afzienbare termijn)
- een aansprekend voorbeeld dat onder de output (paragraaf 7) gerapporteerd is;
- (nieuw) inzicht in randvoorwaarden (buiten kennis&innovatie) die nodig zijn om de missiedoelen te realiseren (denk aan financiering, regelgeving, communicatie, etc).
- het bereiken van (nieuwe) partners en het versterken van opgebouwde netwerken;
- verbinding met (praktijkgericht) onderwijs en andere wijzen van disseminatie;

Geef een link naar de website van het project, video of infographic (indien van toepassing).

Beschrijf de impact van het project, *geef evt. ook een link naar de website van het project, een video of infographic (indien van toepassing)*
The project Mitochondrial Health within TIFN has focussed on evaluating novel food components on mitochondrial metabolism and its relation to muscle health. Cross-sectional studies were used to investigate the relationship between muscle mitochondrial function and muscle health in elderly, whereas large cohort studies were used to investigate the relationship between habitual food consumption and markers of muscle health and physical function. The important studies revealed that there is a clear connection between mitochondrial function and physical outcome parameters mainly skeletal muscle health. These findings are important and suggest that mitochondrial function should be considered a target for the promotion of health with age. Using short-term human intervention studies, the translational aspect of the potential of food components to boost mitochondrial function was tested in an elderly population, with a focus on those volunteers with compromised physical function. Although the human intervention study performed did not yield the expected or hoped outcome, the MitoHealth project layed the basis for future investigations and an experimental design and methodological approach was developed that can be helpful in future studies. For example, several outcome parameters were identified that can be considered as important

read outs both from a mitochondrial perspective (such as exercise efficiency and/or NIRS), but also from a patients' daily-life perspective (measures of muscle strength, muscle coordination). Finally, the project identified novel biomarkers of mitochondrial function that can be applied in observational and intervention studies.

Overall, the project Mitochondrial Health provided the industrial partners with novel insights in the relationship between mitochondrial function and muscle health in elderly, the relationship between nutrient intake/status and (markers of) muscle health and the potential of food components and specific nutrients to prevent, delay or improve aging associated decline and disturbances in muscle health and physical function, by targeting mitochondrial function.

Bijlage 1 MMIP's

KIA: Landbouw, water en voedsel	
MMIP	A1 Verminderen fossiele nutriënten, water en stikstofdepositie
	A2 Gezonde, robuuste bodem en teeltsystemen gebaseerd op agro-ecologie en zonder schadelijke emissies naar grond- en oppervlaktewater
	A3 Hergebruik zij- en reststromen
	A4 Eiwitvoorziening voor humane consumptie uit (nieuwe) plantaardige bronnen
	A5 Biodiversiteit in de kringlooplandbouw
	B1 Emissiereductie methaan veehouderij
	B2 Landbouwbodems, emissiereductie lachgas en verhoging koolstofvastlegging
	B3 Vermindering veenoxidatie veenweide
	B4 Verhoging vastlegging koolstof in bos en natuur
	B5 Energiebesparing, -productie en -gebruik
	B6 Productie en gebruik van biomassa
	C1 Klimaatbestendig landelijk gebied voorkomen van wateroverlast en watertekort
	C2 Klimaatadaptieve land- en tuinbouwproductiesystemen
	C3 Waterrobuust en klimaatbestendig stedelijk gebied
	C4 Verbeteren waterkwaliteit
	D1 Waardering van voedsel
	D2 Gezonde voeding een makkelijke keuze
	D3 Veilige en duurzame primaire productie
	D4 Duurzame en veilige verwerking
	E1 Duurzame Noordzee
	E2 Natuur-inclusieve landbouw, visserij en waterbeheer in Caribisch Nederland
	E3 Duurzame rivieren, meren en intergetijdengebieden
	E4 Overige zeeën en oceanen
	E5 Visserij
	F1 Verduurzamen en kostenbeheersing uitvoeringsprojecten waterbeheer
	F2 Aanpassen aan versnelde zeespiegelstijging en toenemende weersextremen
	F3 Nederland Digitaal Waterland
	F4 Energie uit water
	ST1 Smart Agri-Horti-Water-Food
	ST2 Biotechnologie en Veredeling

Bijlage 2 TRL-categorieën

De detailcategorieën bestaan uit:
TRL 1 – basisprincipes zijn geobserveerd en gerapporteerd
TRL 2 – technologisch concept en/of toepassing is geformuleerd
TRL 3 – kritische functie of karakteristiek is analytisch en experimenteel bewezen
TRL 4 – component of experimenteel model is gevalideerd in laboratoriumomgeving
TRL 5 – component of experimenteel model is gevalideerd in relevante omgeving
TRL 6 – systeem/subsysteem model of prototype is gedemonstreerd in een relevante omgeving
TRL 7 – prototype van het systeem is gedemonstreerd in een operationele omgeving
TRL 8 – daadwerkelijk systeem is compleet en gekwalificeerd door test en demonstratie
TRL 9 – daadwerkelijk systeem is bewezen door succesvol operationeel bedrijf