Lees s.v.p. zorgvuldig de handleiding.
Klik bovenaan de 1e pagina in de cel 'Coordinating investigator 1'. Gebruik de tab-toets om binnen pagina 1 naar een ander veld te gaan. Klik bovenaan de volgende pagina weer in de 1e cel (vraag 1.3) om verder te gaan. Gebruik daarna weer de tab-toets.

LONG FONDS
Voorheen Astma Fonds

Final report

LF 2015
Projectnr:
3.2.09.049

1. General information

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1.3	Title of project:	
	English	Systemic manifestations and co-morbidity in COPD are associated with markers of accelerated aging.
	Dutch	Systemische effecten en co-morbiditeiten in COPD zijn geassocieerd met markers van versnelde veroudering.
	Project number	3.2.09.049
1.4	Time schedule:	
	Start of project	30-12-2010
	Duration of project	48 (months)
	Period of funding	from 30-12-2010 till 30-12-2014
1.5	Grant	€ 250.000
1.6	Short description of the project for public information (in Dutch, see guidelines) (max. 250 words): Het huidige project heeft onderzocht of COPD gekenmerkt kan worden als een syndroom voor versnelde veroudering. Om deze vraagstelling op te lossen, werd een batch van klinische en metabole gegevens van een groep COPD patiënten, rokende en niet rokende controles verzameld. Bij de proefpersonen werd bloed afgenomen en een aantal COPD gerelateerde co-morbiditeiten objectief bepaald. De inclusieperiode liep van januari 2011 tot december 2012. De analyses werden uitgevoerd in 160 patiënten, 38 niet rokende en 82 rokende controle personen. Leeftijd en geslacht was vergelijkbaar tussen de groepen. Momenteel wordt gewerkt aan 3 artikelen aangaande dit onderzoek. Het eerste artikel behandelt de COPD specificiteit van de bepaalde verouderingsmarkers (bloed concentratie of genexpressie data van telomeerlengte, sirtuine, totaal (T) en soluble (S) klotho, Ku70/80, TERF2), rekening houdend met de complexiteit van de ziekte (inflammatie en oxidatieve stress). De resultaten laten zien dat van de markers enkel telomeerlengte onafhankelijk geassocieerd is met longfunctie, zelfs na correctie voor verschillende factoren. Van deze analyse is een artikel geschreven dat bij *Chest* ingediend is voor publicatie. Dit artikel zal verwerkt worden in een proefschrift dat in de tweede helft van dit jaar verdedigd zal worden. De overige hoofdstukken in het proefschrift zijn verkregen van reeds bestaande databases, en deze zijn beschreven in eerdere voortgangsrapportages. Een tweede artikel van het huidige project gaat over de sRAGE en esRAGE concentratie en genexpressie in het beschreven cohort. Het blijkt uit de analyse dat, ondanks sRAGE consistent verlaagd is in COPD, dit niet veroorzaakt wordt door zijn wegvangers ADAM 10 en 17. Dit artikel kan binnenkort gesubmit worden bij Thorax. In het derde artikel wordt de COPD specificiteit van verschillende co-morbiditeiten onderzocht.	

2. Report		
2.1	Summary:	
	Title	Systemic manifestations and co-morbidity in COPD are associated with markers of accelerated aging.
	Authors	Rutten EPA, Reynaert N, Gopal P, EFM Wouters
	Dept./Institute(s)	CIRO+, Horn and MUMC, Maastricht, the Netherlands
	Keywords (max. 6)	Ageing; co-morbidity; oxidative stress; inflammation; pulmonary disease, chronic obstructive

	Abstract (max. 250 words): The present project investigates whether COPD is a syndrome of accelerated ageing. In a group of COPD patients, smoking and never-smoking control subjects, blood will be collected and a number of COPD related co-morbidities (osteoporosis, cardio-vascular stiffness, skeletal muscle wasting, metabolic syndrome) will be objectively diagnosed. The study was started in January 2011 and subject inclusion ended in December 2012. In total, 160 COPD patients, 38 never smoking and 82 smoking (ex or current) smoking control subjects were included for analyses. Age en gender were comparable between groups. From this cohort, three manuscript are being prepared currently. The first manuscript handles about the COPD specificity of a batch of ageing markers (blood concentration or gene expression data of telomere length, sirtuin, total (T) en soluble (S) klotho, Ku70/80, TERF2) in relation to the systemic complexity of the disease. The manuscript shows that only telomere length is independently associated with lung function after multiple correction. This manuscript is submitted to Chest. This manuscript will also be included in a thesis which will be defended in the second half of this year. A second manuscript is about sRAGE and esRAGE concentration and gene expression in the cohort. The results showed that these sheddases are no determinants of sRAGE in the present cohort, and will be submitted to Thorax soon. In addition, a third manuscript evaluates the COPD specificity of the objectively defined co-morbidities.
2.2	Description of original question/aim (max. 150 words): We <u>hypothesized</u> that accelerated aging is a key pathophysiological mechanism of COPD, and that markers of accelerated aging are related to important domains of the disease, particularly to the systemic manifestations of COPD and the clinically manifested co-morbidity. In order to investigate this hypothesis, the following study objectives were formulated: <u>First objective:</u> To objectively diagnose the amount and the severity of co-morbidities (muscle wasting, osteoporosis, cardiovascular risk and glucose intolerance) and systemic manifestation (inflammation and oxidative stress) in a COPD population admitted for pulmonary rehabilitation; <u>Second objective:</u> To determine if COPD can be described as a syndrome of accelerated aging. This objective is tested by the analysis of a panel of biomarkers representing different pathways of the ageing process.
2.3	Results (max. 2500 words, please submit a maximum of 4 figures and diagrams separately): The 160 COPD patients, 38 smoking and 82 never smoking control subjects had comparable age and gender (**Table 1**). The COPD patients had, as defined, significant airflow obstruction, and the number of pack years smoked as well as the number of ex-smokers was higher in patients compared to the smoking controls. Plasma levels of CRP, IL-6, fibrinogen as well as total leukocyte numbers were increased and IL-8 tended to be increased in COPD patients compared to both control groups (data not shown). Plasma uric acid levels and catalase gene expression were not different between the groups, but SOD2 gene expression was significantly lower in the patients compared to both control groups (data not shown). Leukocyte telomere length was on average 300 base pairs (bp) shorter in the COPD group compared to both control groups. Telomere length was not different between the smoking and never smoking control groups. Of the anti-ageing markers, gene expression of sirtuin 1 and Sklotho was significantly lower in the patients compared to the smoking and never smoking controls, and so was Ku70 gene expression, a component of DNA repair. p21 gene expression, a marker of senescence, was increased in the patients compared to the smoking controls. Tklotho, Ku80, TERF2 and p16 gene expression was not different between the groups. Furthermore, the multivariate regression analyses showed that only telomere length and p21 gene expression remained significantly associated with FEV_1/FVC. Telomere length was furthermore independently associated with FEV_1 (**Table 2**). Telomere

	length was also significantly associated with leukocyte numbers, while p21 was associated with IL-6 and catalase gene expression. In contrast, sirtuin 1 mRNA expression was largely determined by number of pack years and smoking status, and Ku70 expression was highly dependent on markers of inflammation (fibrinogen, leukocytes) and anti-oxidant capacity (catalase). No determinants for SKlotho could be identified in the multivariate regression. The analysis of the RAGE pathway confirmed other publications that sRAGE and esRAGE concentration is decreased in COPD patients compared to smoking and never smoking control subjects. Gene expression of Total RAGE is decreased in patients compared to never smoking controls, but expression of membrane nor esRAGE data are different between groups (**Figure 1**). Furthermore, gene expression of the shadasses ADAM 10 and 17 are also decreased in patients compared to smoking and never smoking control subjects. However, the multivariate regression analysis did not show associatation between sRAGE and ADAM 10 or 17, implying that decreased sRAGE levels are not related with ADAM expression. Next, co-morbidity is defined in the present cohort (**Figure 2**). Among the 15 objectively defined co-morbidities, only arterial stiffness, low muscle mass, osteoporosis, symptoms of anxiety and depression and renal failure were COPD specific by binary regression analysis.
2.4	Did the study solve the original question? yes/no (explain) (max. 250 words): Yes. We solved the question whether COPD can be regarded as a syndrome of accelerated ageing. The present analysis confirm consistent alterations of different markers in circulating blood cells of COPD patients. However, taking the heterogeneity of COPD into account, only telomere length remained associated with lung function, suggesting that telomere length is a useful markers to express ageing in relation to lung function. The difference in telomere length between patients and controls was on average 300 bp, indicating that the biological age of a COPD patient is on average about 300 / 40 = 7.5 years older than that of a control subject of the same age. The present data highlight the impact of other (metabolic) confounders on the ageing process. Furthermore, the present project add valuable insight in the complexity of COPD. This is the first study taking so many different markers into account. Additional manuscripts will be prepared to implement these markers in the manifestation of COPD. Indeed, COPD is accepted to be a systemic disease with multiple co-morbidity currently. Defining COPD specific co-morbidity will add additional value to position COPD as a systemic disease, and will eventually lead to more tailored therapy.
3	**Papers (see instructions)**
3.1	All publications (published or submitted peer-reviewed manuscripts): 1. Plasma AGEs and skin autofluorescence are increased in COPD *Accepted by Eur Resp Journal* 2. Association of plasma sRAGE, but not esRAGE with lung function impairment in COPD. *Resp Res* 3. Decreased plasma sRAGE levels in COPD; influence of oxygen therapy. *Eur J Clin Invest* 4. Various mechanistic pathways representing the ageing process are altered in COPD. *Submitted to Chest* 5. Alterations in gene expression of RAGE and its sheddases in blood of COPD patients do not relate to decreased plasma sRAGE levels. *In preparation* 6. COPD specificity of related co-morbidity. *In preparation*
3.2	All publications (not peer-reviewed like abstracts, newspapers, websites, etc.): 1. Soluble receptor for advanced glycation end products are decreased but not the levels of advanced glycation end product N^{ε}-(carboxymethyl)lysine in chronic obstructive pulmonary disease. *Poster presentation during the ATS 2011.* 2. Skin autofluorescence is not a good marker for disease status in COPD. *Presentation during the ERS 2011* 3. Plasma AGEs and skin autofluorescence are increased in Chronic Obstructive Pulmonary Disease and are associated with severity of disease. *Poster presentation*

	during the NRS young investigator symposium 2012 4. Skin autofluorescence and plasma Advanced Glycation End products are increased in Chronic Obstructive Pulmonary Disease. *Poster presentation during ATS 2012* 5. Effect of Hypoxia on Receptor for Advanced Glycation End products and AGEs in lung and circulation. *Poster presentation during the ATS 2013* 6. Accelerated ageing in the ICE-Age study. *Presentation during the 'Longdagen 2014'* *7.* Direct and indirect evidence for accelerated ageing in COPD. *Poster presentation during ERS 2014* *8.* Alterations in gene expression of RAGE and its sheddases in blood of COPD patients do not relate to decreased plasma sRAGE levels. *Poster presentation during ERS 2014*
4.	**Implementation (see instructions)**: Apart from the reductionist approach of COPD, COPD has to be tackled as a systemic disease, needing an holistic approach. This is one of the first studies in which the lung pathology, but also the systemic compartment (systemic inflammation, oxidative stress and co-morbidity) has been taken into account. Therefore, we have a batch of data to incorporate and unravel the complexity of COPD. Hence, despite the broad baseline characterisation which included the present project, all subjects are followed-up for two years as part of a subsequent study. This will allow us to evaluate COPD progression, but also the progression of the systemic manifestation of COPD. By defining more COPD specific features and co-morbidities, better patient tailored therapy will be adopted. Hence, the present study confirms that COPD can be regarded as a syndrome of accelerated ageing. This finding will place other findings in another perspective, in the way that one has to approach patients with COPD slightly different. In addition, since there is a lot of similarity between COPD and the ageing process, it can be questioned whether COPD can be seen as a model of multi-morbidity, and as such, current findings might be extrapolated to other chronic diseases as well. This hypothesis warrants further foundation.

Ondertekening	
Datum: 29-04-2015	Handtekening aanvrager: