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# Health-related quality of life is poor but does not vary with cardiovascular disease burden among patients operated for severe atherosclerotic disease

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ABSTRACT

*Background:* Patients with cardiovascular disease (CVD) are reported to have a poorer health-related quality of life (HRQoL) compared to healthy age- and gender-matched individuals. Moreover, HRQoL seems to predict survival in CVD populations. We studied HRQoL and the association with outcome during follow-up in a population undergoing surgery for peripheral artery disease or cerebrovascular large artery disease.
*Methods:* In the Athero-Express biobank cohort study patients filled in a questionnaire containing RAND-36. We stratified the cohort to compare HRQoL scores (range 0–100, higher scores representing better HRQoL) and assessed three-year event-free survival for composite cardiovascular endpoints of patients with good (above median) versus poor (equal to and below median) HRQoL at baseline. Additionally we compared the cohort to a healthy age-matched population.
*Results:* 2012 and 865 patients undergoing carotid endarterectomy (CEA) or endarterectomy of femoral/iliac arteries (FEA) were included respectively. The median HRQoL was 75 (IQR 0–100 (both patient groups)) for physical role limitations versus 0 (IQR 0–100 (CEA) and 0–66.7 (FEA)) for emotional role limitations. No differences in HRQoL subscores were found, CVD burden did not associate with HRQoL and three-year composite event rates did not associate with the reported HRQoL in both CEA and FEA. Both groups had poor HRQoL scores compared to an age-matched general population, especially regarding emotional role limitations and social functioning.
*Conclusions:* HRQoL is poor and does not associate with CVD burden within patients suffering from severe atherosclerotic disease. Reported HRQoL was not associated with incident cardiovascular events during follow-up.


## 1. Background

Cardiovascular diseases (CVDs) are the world's leading cause of death [1]. The majority of CVDs are caused by atherosclerosis, a systemic inflammatory disease that manifests in different organs including the brain, heart, kidneys and legs. Disease burden of CVD is high as symptomatic atherosclerosis in these organs can be physically as well as mentally disabling. Physical functioning is for example affected by paralysis due to cerebrovascular ischemia, while depression is known to co-occur with cardiovascular diseases [2].

Scoring systems of health-related quality of life (HRQoL), such as RAND-36 (a questionnaire equivalent to SF-36) are developed to measure the subjectively perceived influence of disease on physical, social and emotional functioning [3,4]. Investigating HRQoL in various patient groups is clinically relevant as patients with poor HRQoL might benefit from referral to both occupational therapy for simple practical interventions and psychological support to learn to cope with their emotional and physical problems.

Patients with symptomatic atherosclerosis, such as peripheral arterial occlusive disease [5], carotid artery occlusive disease [6], coronary artery disease [7], abdominal aortic aneurysms [8] and stroke [9], as well as the known risk factors for atherosclerosis, e.g. hypertension [10], diabetes [11] and obesity [12], are reported to have a poorer HRQoL as measured by SF/RAND-36 when compared to healthy age and gender matched individuals even when they are free of symptoms [13]. Patients with risk factors but without overt CVD report declined

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physical HRQoL scores with almost no effect on mental subdomains of HRQoL. Individuals with diagnosed CVD report even lower scores on the physical subdomains with notably declined mental HRQoL scores as well, although social functioning remains largely unaffected. Moreover, compromised quality of life seems to be an independent predictor for survival in CVD populations [14–16].

The purpose of this study is to investigate whether HRQoL differs between people with different cardiovascular disease burdens in a cohort of patients suffering from severe atherosclerotic disease undergoing surgery for peripheral artery disease or cerebrovascular large artery disease. Furthermore cardiovascular event rates during follow-up are compared between groups with differentially reported HRQoL. Additionally we compared the cohort to a healthy age matched population.

We hypothesize that among patients with severe atherosclerotic disease, HRQoL varies depending on cardiovascular disease burden. A negative effect of poor HRQoL on cardiovascular event rates during follow-up is expected. We expect a HRQoL in the patients that is significantly worse than the general population.

## 2. Methods

### 2.1. Population

Since 2002 the Athero-Express biobank study is an ongoing cohort study that includes carotid and femoral endarterectomy patients from two large tertiary vascular referral hospitals in The Netherlands without any exclusion criteria. Upon surgery, atherosclerotic plaques are obtained for histological assessment. To date, over 3000 carotid and femoral endarterectomy patients have been included. In the three years of follow-up time, in which patients are asked to fill in a follow-up questionnaire after 1, 2, and 3 years, approximately 30% of patients reach an endpoint of cardiovascular origin. Study outline and protocol have been described in detail before [17]. Upon inclusion in the Athero-Express biobank study patients are asked to fill in a detailed questionnaire that contains 36 questions from RAND-36. All patients that were included up to September 2013 and completed the questionnaire were included in the present analysis.

### 2.2. Measurement of HRQoL

HRQoL was measured according to the validated Dutch version of RAND-36. Scores on all nine subdomains (physical functioning (PF), social functioning (SF), role limitations due to physical functioning (RP), role limitations due to emotional functioning (RE), mental health (MH), vitality (VT), bodily pain (BP), general health perception (GH) and health change (HC)) were computed to a scale from 0 to 100 with higher scores representing better HRQoL.

HRQoL measures in healthy controls were obtained from the Dutch RAND-36 manual [3]. The manual describes a validation study in a random sample of 1063 citizens of the Dutch municipality of Emmen in 1992. Among others they were stratified by age.

### 2.3. Measurement of cardiovascular disease burden

Cardiovascular disease burden was determined in several ways. Firstly, the symptomatology of the operated artery, e.g. indication for surgery, was determined. Symptomatology of the treated femoral/iliac endarterectomy patients was assessed using the Fontaine classification. For carotid endarterectomy patients were stratified according to inclusion diagnosis (stroke, transient ischemic attack patients, patients with ocular symptoms and asymptomatic patients). Secondly, the presence of different risk factors (age, male sex, obesity, smoking, hypertension, diabetes, hypercholesterolemia) was assessed. Thirdly, the history of a second atherosclerotic organ concomitant to the operated artery (defined by having a history of myocardial infarction, stroke, narrowing carotid artery or peripheral arterial disease) was evaluated. All data were collected from patient files. The presence of risk factors and history of atherosclerotic disease were binned into binary scores (present/absent) as much as possible.

### 2.4. Definition of endpoints

A cardiovascular composite endpoint was defined as having at least one of the following events during follow-up: (fatal) myocardial infarction, (fatal) cerebral infarction or bleeding, coronary angioplasty or coronary artery bypass grafting, peripheral arterial intervention, fatal heart failure, fatal aneurysm rupture, other cardiovascular death, leg amputation or sudden death. Endpoints were collected from validated follow-up of the Athero-Express biobank cohort. For cardiovascular endpoint analyses, HRQoL scores were binned into 'poor' (equal to and below median) and 'good' (above median).

### 2.5. Ethics

All patients provided written informed consent. The study protocol of the Athero-Express biobank study has been approved by the local medical ethics committees.

### 2.6. Statistical analysis

Descriptive statistics were used to analyze the demographics of the population. To explore response bias as a potential confounder, univariate analysis was carried out for associations between baseline characteristics and response rates (chi-square tests for categorical variables and t-tests for continuous variables). p-Values $<0.05$ were considered statistically significant. Because of non-normal distribution of HRQoL scores, nonparametric tests were used to compare HRQoL scores between groups with the absence and presence of risk factors, history of previous (symptomatic) atherosclerotic disease and symptomatology. Dichotomous variables were compared using the Mann–Whitney *U* test, categorical variables were compared using the Kruskal–Wallis test. After correcting for multiple testing (18 tests in each of the 9 HRQoL subdomains) using the Bonferroni correction, p-values $<0.003$ were considered statistically significant. Potential confounders in the relation between symptomatology and any of the nine HRQoL subdomains were identified by ANOVA for continuous variables and linear-by-linear association chi-square tests for categorical variables. Variables with $p < 0.20$ were added to a multivariate regression model. After correcting for multiple testing (nine subdomains in two separate populations) using Bonferroni correction, p-values $<0.003$ were considered statistically significant. Reference sets for the general population were obtained from the RAND-36 manual. To compare survival of good and poor HRQoL, we plotted Kaplan–Meier curves for the composite cardiovascular endpoint stratified to poor and good HRQoLs. Differences between the strata were tested with log rank tests. SPSS version 20 was used for all analyses. The reporting of this study conforms to the STROBE statement [18].

## 3. Results

The current study included 2012 carotid endarterectomy (CEA) patients and 865 patients with endarterectomy of iliac or femoral arteries (FEAs). Of CEA and FEA patients 68% and 72% were male respectively. Age was 69 (range 35–93) (CEA) and 68 (range 30–100) (FEA). Baseline characteristics are shown in Table 1. Loss to follow-up rates were 10.3% in FEA and 9.3% in CEA with median follow-up times of 2.9 years and 3.0 years respectively. In total, 834 patients reached an endpoint of cardiovascular origin, 469 (23%) after CEA and 379 (44%) after FEA.

**Table 1**
Baseline characteristics.

| Operating site | Carotid artery n = 2012 | | Femoral/iliac artery n = 865 |
|---|---|---|---|
| Age (mean) (SD) | 68.96 (9.29) | | 67.64 (9.14) |
| Males (n) (%) | 1376/2012 (68.4%) | | 620/865 (71.7%) |
| BMI (mean) (SD) | 26.40 (3.93) | | 26.28 (8.19) |
| GFR (mean) (SD) | 72.17 (20.70) | | 79.45 (48.51) |
| Smoking (n) (%) | 672/1953 (34.4%) | | 340/844 (40.3%) |
| Hypertension (n) (%) | 1438/1948 (73.8%) | | 623/839 (74.3%) |
| Diabetes (n) (%) | 454/2003 (22.7%) | | 257/862 (29.8%) |
| Hypercholesterolemia (n) (%) | 1240/1832 (67.7%) | | 526/765 (68.8%) |
| History of MI (n) (%) | 408/1987 (20.5%) | | 238/853 (27.9%) |
| History of stroke/TIA (n) (%) | 1272/1889 (67.3%) | | 113/835 (13.5%) |
| Restenosis (n) (%) | 85/1972 (4.3%) | | 139/770 (18.1%) |
| Contralateral stenosis >50% (n) (%) | 809/1786 (45.3%) | | 209/340 (61.5%) |
| History of intermittent claudication (n) (%) | 368/622 (59.2%) | History of narrowing carotid artery (n) (%) | 148/844 (17.5%) |
| Presenting symptom CEA (n) (%) | | Ankle–brachial index operated leg (mean, SD) | 0.59 (0.21) |
| *Asymptomatic | 272/1998 (13.6%) | Fontaine classification for femorals (n) (%) | |
| *Ocular | 310/1998 (15.5%) | *Fontaine IIb | 401/736 (54.5%) |
| *TIA | 876/1998 (43.8%) | *Fontaine III | 184/736 (25.0%) |
| *Stroke | 540/1998 (27.0%) | *Fontaine IV | 151/736 (20.5%) |

Abbreviations: SD = standard deviation, BMI = body mass index, GFR = glomerular filtration rate, MI = myocardial infarction, TIA = transient ischemic attack and CEA = carotid endarterectomy.

### 3.1. Response rates

The response rates for the RAND-36 were 68% (n = 1374) for CEA and 63% (n = 548) for FEA. There were no significant differences between responders and non-responders on baseline characteristics in both groups (data not shown). Event-free survival between responders and non-responders did not differ within CEA or FEA patient groups (data not shown).

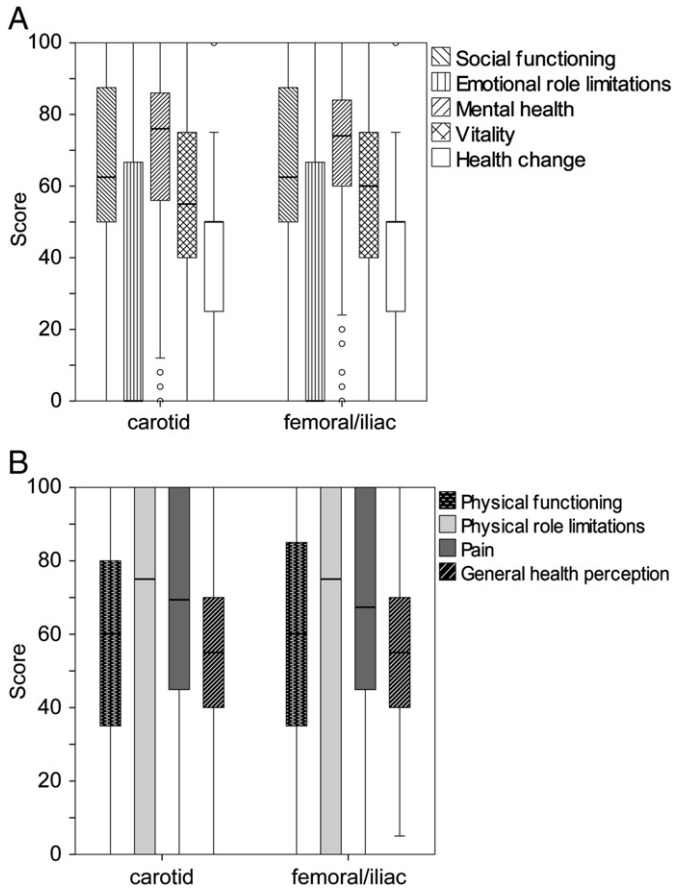


**Fig. 1.** Health-related quality of life scores, stratified by operating site. Carotid: carotid endarterectomy patients, and femoral/iliac: femoral/iliac endarterectomy patients.

### 3.2. Health-related quality of life scores

HRQoL scores did not differ between CEA and FEA patients (Fig. 1). In both disease groups, no difference in any of the HRQoL subdomains was observed between patients with different cardiovascular disease burdens. Firstly, HRQoL did not differ on the basis of symptomatology (Fig. 2a and b). Data are shown for PF and RE as PF was unexpectedly

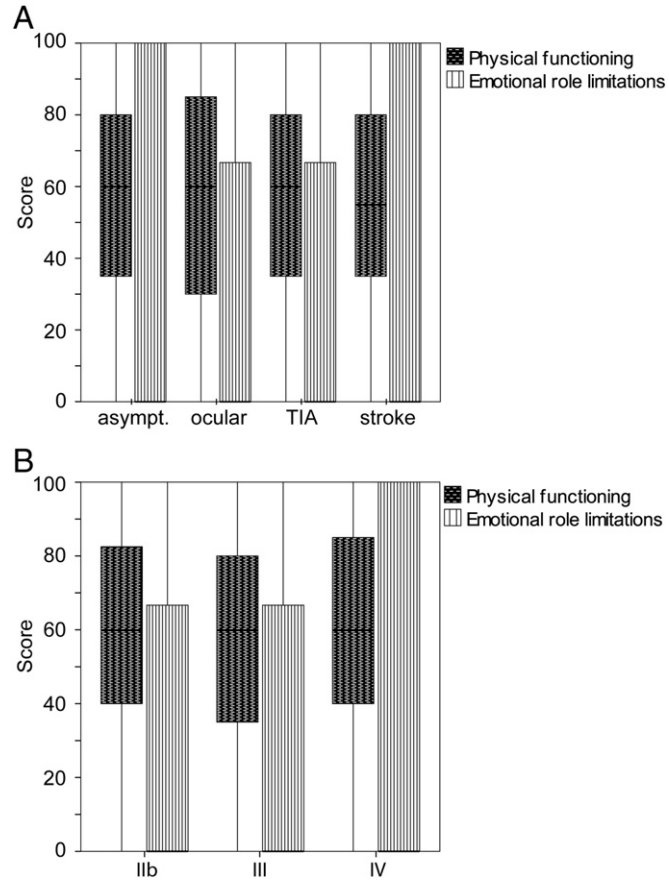


**Fig. 2.** Health-related quality of life scores, stratified by symptomatology. A: inclusion diagnosis for carotid endarterectomy patients and B: Fontaine classification for femoral/iliac endarterectomy patients; abbreviations: asympt = asymptomatic and TIA = transient ischemic attack.

high even in Fontaine IV and stroke patients whereas RE was unexpectedly low across all groups. Secondly, no difference was found between patients with and without common risk factors such as male sex, age, hypertension, diabetes, smoking, hypercholesterolemia or obesity (data not shown). Secondly, no difference was found between patient groups with and without a history of cardiovascular disease (Supplemental Table 2). Correction for potential confounding factors did not alter the results.

Event rates were not influenced by below median scores on any of the subdomains of HRQoL in both CEA and FEA patient groups (Supplemental Table 3). Data are shown in Fig. 3 for SF and RE because these subdomains differed most from the reference population (see Section 3.3).

### 3.3. Comparison with general population

Athero-Express patients (both CEA and FEA) report a poor HRQoL compared to healthy Dutch age-matched individuals (Table 2). The decline ranges from 5 points (MH, BP, GH, HC) to 50 points (RE) on a scale from 0 to 100. In the general population, HRQoL declines with age, especially in the physical subdomains. On all subdomains, both CEA and FEA patients in the Athero-Express cohort report a lower HRQoL than 85-year old control subjects. The subdomains that are particularly affected are SF and RE.

## 4. Discussion

According to RAND-36 health-related quality of life is poor, but no differences were observed between subgroups of a severely atherosclerotic population with carotid or femoral stenosis undergoing surgery. Furthermore, HRQoL was not associated with event-free survival during three years of follow-up in both patient groups.

One possible explanation is that all Athero-Express patients have a severe symptomatic type of atherosclerosis, leading to an equally poor HRQoL across the burden groups. Furthermore, Athero-Express patients are all operated on and because of stringent protocols for carotid endarterectomy (surgery within two weeks after the cerebral event) some are only recently confronted with this life threatening disease and the need for vascular surgery, which could lead to emotional distress. This could especially account for the poor scores on functioning due to emotional role limitations in both Athero-Express populations, also when compared to the general population. Depression, known to be of high incidence in patients with CVD, seems to fit this finding less as a cause since scores on mental health were nearly unaffected compared to the general population.

Comparison of outcomes of the HRQoL scores of the Athero-Express biobank study remains suboptimal. Firstly, the RAND-36 HRQoL questionnaire is being replaced by SF-36 in current literature. The SF-36 and RAND-36 are roughly, but not totally comparable (bodily pain and general health are calculated differently). Secondly, researchers tend to display their outcomes in graphs that do not contain the actual scores, making extraction of data a challenging expedition. Thirdly, both RAND-36 and SF-36 scores are often presented as means with standard deviations, which cannot be interpreted correctly since the outcome of both questionnaires is not normally distributed. In this way, information is lost and a proper comparison is impossible.

When compared to other (SF-36) CEA patient cohorts, patients of the Athero-Express biobank operated on carotid arteries exhibit poor HRQoL scores on functioning to emotional role limitations, whereas impact on role limitations due to physical functioning is relatively low. Stolker et al. [19] for example report a 20 point lower HRQoL score in the RP subdomain at baseline than the Athero-Express patients. This could be explained by the selection of "high risk" CEA patients in their SAPPHIRE study. However, Cohen et al. [20] (CREST study group) report a 10 point lower HRQoL score on RP and a 40 point higher score on RE. Strikingly, because both cohorts contain more asymptomatic patients than the Athero-Express cohort (70% and 47% respectively), they are

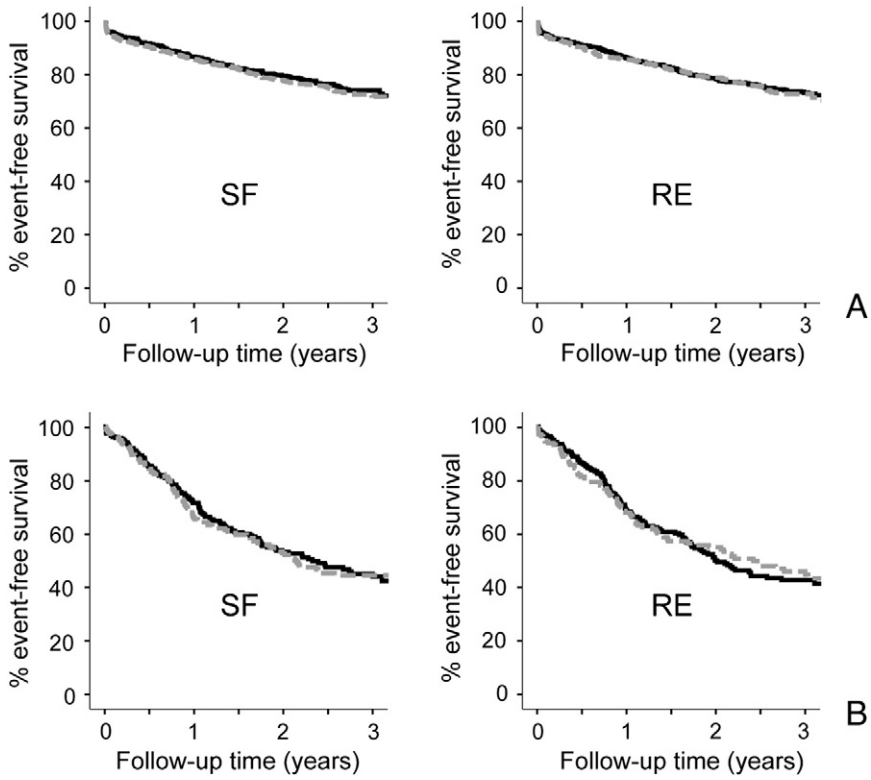


**Fig. 3.** Three year event-free survival for good and poor HRQoL. A: carotid artery endarterectomy patients and B: femoral/iliac artery endarterectomy patients; continuous black line: HRQoL above median and dotted gray line: HRQoL equal to and below median; abbreviations: SF = social functioning and RE = role limitations due to emotional functioning.

**Table 2**
Comparison of HRQoL with the Dutch general population.

| | Dutch reference population | | | | AE carotid artery | | AE femoral/iliac artery | |
|---|---|---|---|---|---|---|---|---|
| | Age 55–64 | Age 65–75 | Age 75–85 | Age 85 + | Mean age: 69 | | Mean age: 68 | |
| | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Median (IQR) | Mean (SD) | Median (IQR) |
| Physical functioning | 72.7 (24.4) | 66.7 (26) | 56.0 (26.0) | 60.0 (31.8) | 55.7 (28.8)* | 55 (35–80) | 57.7 (28.6) | 60 (35–85) |
| Social functioning | 86.6 (21.4) | 83.2 (23.7) | 82.0 (24.9) | 75.1 (31.1) | 63.1 (28.6)* | 62 (50–87.5) | 66 (28.4)* | 62.5 (50–87.5) |
| Role limitations, physical | 76.5 (38.1) | 69.1 (42.5) | 60.1 (43.1) | 76.6 (35.9) | 56 (44) | 75 (0–100) | 54.6 (44.2)* | 75 (0–100) |
| Role limitations, emotional | 90.1 (24.5) | 82.9 (33.8) | 73.7 (40.4) | 82.4 (39.3) | 33.2 (43.1)* | 0 (0–100) | 32.6 (43)* | 0 (0–66.7) |
| Mental health | 77.1 (18.7) | 75.9 (17.3) | 76.9 (14.3) | 78.3 (15.7) | 70 (20.3) | 72 (56–84) | 70.9 (19) | 72 (60–84) |
| Vitality | 67.0 (21.3) | 64.2 (22.0) | 60.1 (21.3) | 67.5 (23.2) | 54.6 (22.4)* | 55 (40–70) | 56.5 (20.7)* | 60 (40–70) |
| Pain | 74.7 (25.0) | 74.8 (28.0) | 72.0 (30.3) | 77.3 (26.7) | 68.5 (28.7) | 69.4 (44.9–100) | 69.5 (28) | 68.4 (44.9–100) |
| General health perception | 64.4 (22.2) | 60.1 (23.9) | 59.0 (21.2) | 61.4 (21.3) | 54.6 (20.1) | 55 (40–70) | 55.8 (19.5) | 55 (40–70) |
| Health change | 48.7 (15.4) | 46.8 (20.5) | 45.1 (18.7) | 50.0 (0.0) | 40.1 (27.0) | 50 (25–50) | 41.8 (25.1) | 50 (25–50) |

Abbreviations: SD = standard deviation, IQR = interquartile range and * = $p < 0.001$ compared to age matched group.

thus expected to have a higher HRQoL on the physical subdomains, not lower. Two different European studies exhibit the same pattern. A British study [21] with 13% asymptomatic patients (equal to the Athero-Express cohort) reports RE that is 30 points higher than Athero-Express patients while RP is 20 points lower. The Serbian cohort of Vlajinac et al. [22] with 35% stroke patients reported an excellent PF (71.7) at baseline but the same pattern exists within the role limitation subdomains: lower PF and higher RE than Athero-Express patients (−15 and +15 points respectively). All cohorts, including the Athero-Express cohort, have a mean age of around 70.

Mazari et al. [23] recorded SF-36 scores in 178 patients that were about to undergo femoropopliteal angioplasty (median age 70) and Van Hattum et al. [24] report HRQoL scores of 1001 patients (mean age 62) before peripheral bypass surgery. Compared to these cohorts, Athero-Express FEA patients differ in the same way as Athero-Express CEA patients do: a poor score on RE with relatively high RP. There is no clear explanation for the differences found in functioning due to role limitations.

A possible limitation of the Athero-Express biobank study regarding HRQoL is the fact that the Athero-Express population only consists of patients that have undergone surgery, leading to selection bias of patients that are physically able to handle the procedure. Even more severely disabled patients are thus excluded, leading to a possible overestimation of the actual HRQoL. However, as inclusion of non-operable patients would further lower the scores, this would probably not affect the already observed 'floor effect'.

Non-response on the RAND-36 is not thought to influence the outcome either, because response rates did not differ with cardiovascular disease burden. Only patients with a second affected peripheral artery had consistently lower response rates in CEA and FEA, but this difference did not reach significance. This could however implicate that more severely disabled patients may not have filled in the questionnaire. Since survival rates did not differ between responders and non-responders in both CEA and FEA patients, impact on survival is not to be expected.

Another possible confounder is socio-economic status, for it is known that patients with a low socio-economic status experience a significantly lower health-related quality of life compared to patients with a high socio-economic status [25]. This difference could well be explained by education. Both factors are not measured in the Athero-Express biobank, so they could not be corrected for and may have introduced confounding.

Atherosclerotic disease affecting the cerebrovascular and peripheral arteries has a large impact on HRQoL, independent of risk factors or medical history. Considering the systemic nature of the disease and the lack of options to completely abolish atherosclerotic plaque burden in individual patients, treatment should include the improvement of HRQoL. Health care specialists that work with patient groups affected by atherosclerosis therefore need to be aware of the poor quality of life of their patients to be able to offer practical physical and emotional support or detect more severe mental health issues that need attention from psychological experts.

## 5. Conclusion

Using RAND-36, HRQoL is poor, especially regarding emotional and social functioning, but cardiovascular disease burden does not influence HRQoL within patients suffering from severe atherosclerotic disease undergoing surgery. In addition, reported quality of life was not associated with incident cardiovascular events during follow-up.

## Funding sources

None.

## Conflict of interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijchv.2014.07.001.

## References

[1] WHO. Causes of death, summary tables; 2011 [Geneva, Switzerland].
[2] Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. Eur Heart J 2014;35(21):1365–72.
[3] van der Zee KI, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36, een handleiding. 2nd rev ed. UMCG/Rijksuniversiteit Groningen, Research Institute SHARE; 2012.
[4] VanderZee K, Sanderman R, Heyink JW, de Haes H. Psychometric qualities of the RAND 36-Item Health Survey 1.0; a multidimensional measure of general health status. Int J Behav Med 1996;3:104–22.
[5] Maksimovic M, Vlajinac H, Marinkovic J, Kocev N, Voskresenski T, Radak D. Health-related quality of life among patients with peripheral arterial disease. Angiology 2013;65(6):501–6.
[6] Bakker FC, Klijn CJM, van der Grond J, Kappelle LJ, Jennekens-Schinkel A. Cognition and quality of life in patients with carotid artery occlusion: a follow-up study. Neurology 2004;62:2230–5.
[7] Dickens C, Cherrington A, McGowan L. Depression and health-related quality of life in people with coronary heart disease: a systematic review. Eur J Cardiovasc Nurs 2012;11:265–75.
[8] Mouawad NJ, Leichtle SW, Manchio JV, Lampman RM, Halloran BG, Whitehouse WM. Construct domain analysis of patient health-related quality of life: physical and mental trajectory profiles following open versus endovascular repair of abdominal aortic aneurysm. Patient Relat Outcome Meas 2013;4:1–6.
[9] De Weerd L, Luijckx G-JR, Groenier KH, van der Meer K. Quality of life of elderly ischaemic stroke patients one year after thrombolytic therapy. A comparison between patients with and without thrombolytic therapy. BMC Neurol 2012;12:61.
[10] De Carvalho MV, Siqueira LB, Sousa ALL, Jardim PCBV. The influence of hypertension on quality of life. Arq Bras Cardiol 2013;100:164–74.
[11] Wermeling PR, Gorter KJ, van Stel HF, Rutten GEHM. Both cardiovascular and non-cardiovascular comorbidity are related to health status in well-controlled type 2 diabetes patients: a cross-sectional analysis. Cardiovasc Diabetol 2012;11:121.

[12] Ul-Haq Z, Mackay DF, Fenwick E, Pell JP. Meta-analysis of the association between body mass index and health-related quality of life among adults, assessed by the SF-36. Obesity (Silver Spring) 2013;21:E322–7.
[13] Verbraak ME, Hoeksma AF, Lindeboom R, Kwa VIH. Subtle problems in activities of daily living after a transient ischemic attack or an apparently fully recovered non-disabling stroke. J Stroke Cerebrovasc Dis 2012;21:124–30.
[14] Saquib N, Brunner R, Kubo J, Tindle H, Kroenke C, Desai M, et al. Self-perceived physical health predicts cardiovascular disease incidence and death among postmenopausal women. BMC Public Health 2013;13:468.
[15] Issa SM, Hoeks SE, Scholte op Reimer WJM, van Gestel YR, Lenzen MJ, Verhagen HJ, et al. Health-related quality of life predicts long-term survival in patients with peripheral artery disease. Vasc Med 2010;15:163–9.
[16] Kato N, Kinugawa K, Seki S, Shiga T, Hatano M, Yao A, et al. Quality of life as an independent predictor for cardiac events and death in patients with heart failure. Circ J 2011;75:1661–9.
[17] Verhoeven BAN, Velema E, Schoneveld AH, de Vries JP, de Bruin P, Seldenrijk CA, et al. Differential atherosclerotic plaque expression of mRNA and protein in relation to cardiovascular events and patient characteristics. Rationale and design. Eur J Epidemiol 2004;19:1127–33.
[18] Von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–9.
[19] Stolker JM, Mahoney EM, Safley DM, Pomposelli FB, Yadav JS, Cohen DJ. Health-related quality of life following carotid stenting versus endarterectomy: results from the SAPPHIRE (Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy) Trial. JACC Cardiovasc Interv 2010;3:515–23.
[20] Cohen DJ, Stolker JM, Wang K, Magnuson EA, Clark WM, Demaerschalk BM, et al. Health-related quality of life after carotid stenting versus carotid endarterectomy: results from CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial). J Am Coll Cardiol 2011;58:1557–65.
[21] Lloyd AJ, Hayes PD, London NJM, Bell PRF, Naylor AR. Does carotid endarterectomy lead to a decline in cognitive function or health related quality of life? J Clin Exp Neuropsychol 2004;26:817–25.
[22] Vlajinac H, Marinkovic J, Maksimovic M, Kocev N, Vasiljevic N, Backovic D, et al. Health-related quality of life among patients with symptomatic carotid disease. Postgrad Med J 2013;89:8–13.
[23] Mazari FAK, Carradice D, Rahman MN, Khan JA, Mockford K, Mehta T, et al. An analysis of relationship between quality of life indices and clinical improvement following intervention in patients with intermittent claudication due to femoropopliteal disease. J Vasc Surg 2010;52:77–84.
[24] Van Hattum ES, Tangelder MJD, Lawson JA, Moll FL, Algra A. The quality of life in patients after peripheral bypass surgery deteriorates at long-term follow-up. J Vasc Surg 2011;53:643–50.
[25] Mielck A, Vogelmann M, Leidl R. Health-related quality of life and socioeconomic status: inequalities among adults with a chronic disease. Health Qual Life Outcomes 2014;12:58.