REVIEW

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High Intensity Interval Training in CHD-Patients with Chronic Heart Failure (CHF-HFrEF)

Hochintensives Intervalltraining bei Patienten mit koronarer Herzerkrankung (KHK) mit Herzinsuffizienz (CHF-HFrEF)

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Summary

› **Introduction:** Applicability and effectiveness of high intensity interval training currently being discussed and investigated as a possible addition to moderate continuous training (MCT) for patients with CHF-HFrEF especially in cardiac rehabilitation (CR). Meanwhile, a prospective multi-centre-RCT and meta-analyses are also available for high intensity interval training.
› **Method:** We conducted a selective literature search until December 2017. This was focussed on studies to evaluate high-intensity interval-training modalities in CR in patients with CHF-HFrEF.
› **Results:** While early (and often small) studies with a great variety in exercise-intensity and -protocol-modalities and following meta-analyses often showed highly significant positive results with regard to the maximum oxygen uptake ($\dot{V}O_2$peak) and other relevant clinical parameters, current prospective multicentre RCTs show no such significant advantages for high intensity training compared to MCT.
› **Discussion:** High intensity training in CR phase II and III is a equivalent form of exercise for CHF-HFrEF patients showing equivalent improvement of cardiovascular protection factors, clinical CHF-parameters and quality of life compared with MCT. High-intensity interval training may be applied in stable CHF-HFrEF-patients who tolerate MCT well and in whom further improvement in exercise capacity is aimed. Nevertheless, there is still a need for research in a more precise clinical-application and its long-term effects.

Zusammenfassung

› **Einführung:** Hochdosiertes Ausdauertraining in der Rehabilitation (CR) von Patienten mit Herz-Kreislauferkrankungen werden derzeit als mögliche Addition zum klassischen moderaten kontinuierlichen Ausdauertraining (MCT) diskutiert und erforscht. Aktuell liegen auch erstmalig RCTs und Metaanalysen bei Patienten mit CAD und CHF-HFrEF vor.
› **Methode:** Wir führten eine selektive Literaturrecherche bis Dezember 2017 durch. Das Review widmet sich hochintensivem Intervalltraining bei Patienten mit CHF-HFrEF.
› **Ergebnisse:** Während frühe (oft kleine) Studien mit unterschiedlichen Trainingsintensitäten und -protokollen und folgende Meta-Analysen z. T. hochsignifikant positive Resultate im Hinblick auf die maximale Sauerstoffaufnahme ($\dot{V}O_2$peak) und weitere klinisch relevante Parameter ergaben, kann ein aktuelles prospektives Multicenter-RCT keine signifikanten Vorteile für hochintensives Intervalltraining im Vergleich zum MCT mehr nachweisen.
› **Diskussion:** Die Anwendung von hochintensivem Intervalltraining stellt bei CHF-HFrEF-Patienten eine in Bezug auf die Verbesserung kardiovaskulärer Schutzfaktoren, klinischer Herzinsuffizienz-Parameter und Lebensqualität dem MCT gleichwertige Trainingsform dar. Hochintensives Intervalltraining kann bei klinisch stabilen CHF-HFrEF-Patienten, die das MCT gut tolerieren, eingesetzt werden, wenn eine weitere Steigerung der Leistungsfähigkeit erzielt werden soll. Dennoch gibt es weiterhin erheblichen Forschungsbedarf, insbesondere zur differenzierteren Anwendung und zu Langzeit-Effekten.

KEY WORDS:
Cardiac Rehabilitation, Exercise, Endurance Training, Chronic Heart Failure, High Intensity Interval Training

SCHLÜSSELWÖRTER:
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Introduction

The first part of this review describes principles, definition, history and application of interval training in CHD patients with normal/maintained left-ventricular ejection fraction, part two discusses the relevance of high-intensity interval training, including HIIT/AIT (high-intensity interval training/aerobic interval training) in patients with reduced left-ventricular ejection fraction (chronic heart failure, heart failure with reduced ejection fraction, CHF-HFrEF) based on the results of a selective literature search.

Physical exercise is counted among the clinically-proven primary treatment forms for patients with CHF-HFrEF. Described for the first time nearly 40 years ago, the value of training intervention has been repeatedly proven and meanwhile has become a standard therapy form in secondaryandtertiarypreventionofthisprognostically-relevant disease (3, 21, 28, 32, 39).

Improvements in physical work capacity, quality of life, neurohumoral activation and numerous parameters of muscle and vascular physiology including endothelial function have been demonstrated (23, 31, 40, 43). Physical exercise, performed as moderate continiuous training (MCT) is an established component of training intervention in CHF-HFrEF patients and is recommended as standard therapy in guidelines of the leading specialist societies (4, 29, 30, 44).

The interval training method as such as well as high-intensity interval training, which has been applied for many years in ambitious leisure and performance sports, has attracted the attention of scientific studies in cardiovascular diseases since the 1990s thanks to the observed effects on muscle and vascular physiology.

As early as the 1990s, Meyer et al. (22, 24) gained initial experience with interval training in patients with CHF-HFrEF. The interval training protocols (30/60 sec) determined with the steep ramp test (SRT) showed for training between 17 and 35 minutes at 50% peak work an effective exercise ("pedal-time") of only 5 to 8 minutes. It was shown that hereby low values for the subjective feeling of exertion (RPE-Borg-Skala), a lower rate-pressure product as an expression of cardiac work as well as lower catecholamine levels despite elevated lactate levels were attained (22). The peripheral stimulation was thus higher with concurrently reduced cardiac stress. This principle is advantageous and desirable for chronic diseases like CHF-HFrEF to prevent peripheral deconditioning ("muscle-waste-syndrome") (23). The significantly better prognosis for CHF-HFrEF patients with eliminated or reduced weight loss was explained by the preservation of muscle mass as a relevant part of body weight. Interval training is characterized by the alternating of exercise and recovery phases.

A precise description of this and HIIT/AIT is given in Part 1 of this review.

To date, studies on interval training in CHF-patients have mostly been performed on patients with reduced ejection fraction (HFrEF).

Currently, no study results are available on patients with symptoms of heart failure with preserved ejection fraction (HFpEF). The results especially of the first multicenter RCTs (Ex-DHF and OptimEx) are still outstanding (8, 37). In a pilot study, moderate strength-endurance training brought positive effects in the improvement of diastolic function (7).

High-Intensity Interval Training in Patients with Chronic Heart Failure (CHF) with Reduced Ejection Fraction (HFrEF)

At the beginning of the last decade, Nechwatal et al. studied the effectiveness of interval training with short intensive exercise compared to MCT in HFrEF patients during a 3-week CR. The results showed both training modalities to be equally effective in improving physical work capacity (27). This result was confirmed in another prospective study with significant improvements in maximum work capacity measured in both watts and as $\dot{V}O_2$peak (6).

Later, a Greek research team examined the effects of interval training in CHF-HFrEF patients using the Meyer protocol with and without additional strength training. No adverse events were observed. In both studies published on this topic, a still significantly higher or about doubled increase in $\dot{V}O_2$peak was found in a combination of the two training modalities and additive strength training (2, 38). In another randomized study, interval training at 50-80% of the maximum performance determined by STR in the Meyer method was compared with MCT during an 8-week CR Phase II in CHF-HFrEF patients. Here, too, no adverse events occurred. The $\dot{V}O_2$peak improved significantly by 27% in the interval group while it remained unchanged in the MCT group (11).

Great notice was taken of the results of the "milestone" study, published in 2007 by Wisløff et al., which are still being controversially discussed (31, 43). They show a significantly greater improvement in $\dot{V}O_2$peak from 13.0±1.6 to 19.0±2.1ml/kg/min in a treadmill AIT (4x4-protocol; 90-95% HR_{max}) compared to MCT (13.1±1.1 to 14.9±0.9ml/kg/min). Moreover, a significant increase in left-ventricular ejection fraction in the sense of reverse cardiac remodeling only in the AIT group was disclosed for the first time (43). Another prospective study confirmed significant improvements in the $\dot{V}O_2$peak and other parameters of respiratory efficiency only in the AIT group (41).

While improvement in work capacity is foremost in ambitious leisure and performance sports among athletes, the physical work capacity under everyday conditions is most important for patients with CHF-HFrEF to maintain quality of life, avoid rehospitalization and, where possible, improve the prognosis. High-intensity interval protocols are tolerated by patients with CHF-HFrEF very differently and not always without problems in the authors' own clinical experience. The protocol used by Wisløff (10 min warm-up at 60-70% of HR_{max}, 4x4 min intervals at 90-95% of HR_{max} followed by 4x3 min active recovery at 50-70% of HR_{max}, duration of the session 38 min) is used in some of the available scientific studies and particularly in current multicenter studies on CHD and CHF (43).

The results of a current meta-regression analysis of 55 training studies (n=7553 patients with CHD and CHF) in CR confirm that the effectiveness of the intervention in CR (on average $\dot{V}O_2$peak +3.33 mL/kg/min (+17%)) is influenced decisively by training intensity but not by other factors, including training modality. The effects in studies which included CHF patients ($\dot{V}O_2$peak +3.94 mL/kg/min) were higher than those of CHD patients without included CHF (+2.79mL/kg/min). Training intensity (% $\dot{V}O_2$peak or % HR_{max}) higher by 10% was associated on average with greater improvement in $\dot{V}O_2$peak by 1 mL/kg/min. Despite the large number of patients, no relevant adverse events were reported (40). The results confirm the observations of earlier reviews with respect to the importance of training intensity and duration of the program (especially more than 6 months) in training interventions in CHI patients (1, 19).

The effectiveness of high-intensity interval training compared to MCT in patients with CHF-HFrEF has already been evaluated in two meta-analyses (16, 35). One of these meta-analyses included exclusively studies which compared MCT with interval training, of which in turn, only some contained no other intervention components of CR. In the comparison, high-intensity interval training resulted in a significantly greater increase in $\dot{V}O_2$peak of +2.14 ml/kg/min, whereas there was no difference with respect to a reverse cardiac remodeling or improvement in left-ventricular ejection fraction at rest (16).

The second meta-analysis included studies on combined interval and strength training, exclusively interval training and exclusively MCT compared to inactive control groups. A combination of strength training and HIIT was superior to high-intensity training alone or MCT with respect to ›

Table 2

Summary of the results of current meta-analyses, in which the effectiveness of high-intensity interval training (INT) versus moderate continuous training (MCT) is compared in healthy individuals and CHD patients. CHF-HFrEF=chronic heart failure with reduced ejection fraction; CON=control group; INT=interval training; MCT=moderate continuous training; VCO_2=carbon dioxide production; VE=minute ventilation; VO_2peak=peak oxygen uptake).

META-ANALYSIS	DISEASE	STUDIES INCLUDED	SUBJECTS (N)	AGE (YRS)	STUDY SELECTION	OBJEKTIVES	RESULTS	CONCLUSION (ABSTRACT)
Haykowsky et al., 2013 (16)	CHF-HFrEF	7	567	47-77 (61±9)	comparison of INT and MCT only VO_2max assessed pre- and post-training training period ≥3 weeks	VO_2max (ml/kg/min) LV-EF at rest (%)	VO_2max 2.14 (0.66 -3.63) ml/kg/min LV-EF at rest inconclusive 3.29 (-0.7 -7.28)%	in clinically stable patients with HFrEF, INT is more effective than MCT for improving peakVO_2 but not the LVEF at rest
Smart et al., 2013 (35)	CHF-HFrEF	13	732	46-77	INT: at least 3 bouts of exercise ≤5 min with ≤5 min rest period VO_2max assessed pre- and post-training training period ≥3 weeks	1. changes in VO_2max INT vs. sedentary CON vs. MCT vs. combined INT and RT 2. VE/VCO_2 slopes INT vs sedentary CON vs MCT	VO_2max (mL/kg/min) INT vs. CON 1.58 [1.13, 2.04] VO_2max (mL/kg/min) INT vs. MCT 1.04 [0.42, 1.66] VO_2max (mL/kg/min) INT vs. COMB -1.10 [-1.83, -0.37] VE/VCO2 slope INT vs CON -1.50 [-2.64, -0.37] VE/VCO_2 slope INT vs MCT -1.35 [-2.15, -0.55]	combined strength and intermittent exercise appears superior for peakVO_2 changes when compared to intermittent exercise of similar exercise energy expenditure

the $\dot{V}O_2$peak ($\dot{V}O_2$peak -1.10 ml/kg/min). There was a positive correlation between the weekly energy expenditure and the $\dot{V}O_2$peak. (r=0.48) (35).

Later, the results of another randomized study on combined high-intensity interval training at 100% $\dot{V}O_2$max and 30 sec passive recovery phases combined with strength training over 12 weeks vs. an inactive control group were published. Significant improvements were observed in $\dot{V}O_2$max, maximum performance achieved (watts) and 6-minute-walking distance (5).

A study initiated a short time ago is currently investigating the effects of high-intensity interval training on the quality of life in CHF-HFrEF patients, which is often greatly impaired (41).

Table 1 shows a summary of the results of randomized studies in which the effectiveness of high-intensity interval training was compared to MCT in CHF-HFrEF patients.

Table 2 shows a summary of the results of current meta-analyses, in which the effectiveness of high-intensity interval training is compared to MCDT in CHF-HFrEF patients.

Results of a current Norwegian study (n=4846) confirm a lower risk of cardiovascular events during aerobic endurance training in CR Phase II and III. During the 7-year observation period, a risk of cardiac arrest of 1:58607 training units (TU) (total 3 cases) was determined in 175,820 TU. One of the 3 cases occurred at moderate training intensity (with lethal outcome, risk 1:129,456 TU) and 2 cases at high training intensity (neither with lethal outcome, risk 1:23,182 TU) (26,33). In one study, a significant reduction in the occurrence of arrhythmias was observed in the Holter-ECG after high-intensity interval training compared to MCT resp. the control groups (20).

The goal of the first and thus far only randomized-prospective multicenter study (SMARTEX-HF) (n=261; LV-EF ≤ 35%) was to examine in larger cohorts the effectiveness of the 4x4-min protocol (90-95% HR_{max}) (AIT) compared to MCT at 60-70% HF_{max} or to the usual recommendation of regular exercise (RRE) over 12 weeks. The primary endpoint was the end-diastolic left-ventricular diameter in the context of remodelling; the secondary endpoint was the change in LV-EF, in brain-natriuretic-peptides (BNP), in the quality of life and in $\dot{V}O_2$peak (9).

Compared to the RRE as control group, the primary endpoint was not achieved by either AIT or MCT (LVEDD-Median: AIT: -2.8 mm vs. RRE (p=0.02), MCT -1.6 mm vs. RRE (p=0.34)). This was true also of the comparison of the two interventions with one another (AIT -1.2 mm vs. MCT (p=0.45)). With respect to the LV-EF, there were no significant differences among the three groups. Both interventions led to a significant increase in the $\dot{V}O_2$peak. The difference between the training groups, however, was not significant. Compared to RRE, on the other hand, the difference was significant (Median AIT +1.4 ml/kg/min (p=0.02), MCT+1.8 ml/min/kg (p=0.003)). The changes attained could not be stabilized in the 52-week follow-up. As in the SAINTEX-CHD study on CHD patients with preserved LV-function, the authors determined that more than 50% of the patients in the AIT group did not achieve the target intensity in training, whereas 80% of the MCT group trained at higher intensities than targeted (9).

With respect to relevant adverse events, there were no differences during the intervention, however, in the follow-up phase in this high-risk subject collective there was numerically a trend, to more non-lethal and lethal events for AIT (non-lethal vs. lethal: 32 vs. 3; p=0.10) and RRE (26/1) compared to MCT (8/3), but the differences were not significant. The authors conclude that MCT should remain the standard for training intervention in CHF-HFrEF patients, even in a supervised CR setting (9).

In recent years, both numerous investigators and users have reported problems in adhering to the training targets in the 4x4 min protocol (AIT). By contrast, a Franco-Canadian team observed greater acceptance of short HIIT intervals of up to one minute at >85% HR_{max} and passive recovery in CHF-HFrEF patients, with a concurrent significant improvement in $\dot{V}O_2$peak/$watt_{max}$ (13,15,25). At present, there does not appear to be a universally-applicable protocol for interval training including AIR/HIIT for all CHF-HFrEF patients.

Which program is suitable is determined primarily by the level of training status, resp. an existing deconditioning, the time at which CR was started, comorbidities and the rhythm (in)stability. Especially shortly after an acute disease or deconditioning and in arrhythmias, training stimuli should be gradually dosed, even for MCT, and reevaluated at shorter intervals. Recommendations of some teams are available applying subjective parameters (rate of perceived exertion (RPE) multiplied by training time, "SessionRPE") or objective measurements of heart rate and lactate profiles during the ergometric entry examination. Using heart rate as the only parameter to control training is considered inadequate, especially in the possible presence of chronotopic incompetency in CHF-HFrEF (10,17,18,42) These recommendations have as yet, however, not found essential application in everyday clinical practice.

Conclusions on High-Intensity Interval Training Including AIT/HIIT in Patients with CHF-HFrEF

1. High-intensity interval training can be optionally integrated gradually in the training program as part of CR in addition to MCT on an individual basis, taking into account the individual patient's preferences, physical exercise capacity and other comorbidities to be heeded, especially cardiac arrhythmia, in stable and optimally-treated CHF-HFrEF. HIIT has not to date been associated with a generally higher risk than the generally accepted MCT in stable patients.
2. MCT remains the standard for endurance training of CHF-HFrEF patients, high-intensity interval training incl. HIIT/AIT can be prescribed in addition to MCT, if MCT is well-tolerated and a further increase in performance capacity is to be achieved.
3. SMARTEX-HF, the first multicenter RCT study with a 12-month follow-up, indicates that there may possibly be a "too much" or an overdose of physical activity, especially in high-risk collectives like CHF-HFrEF patients.
4. In the context of phase II CR, the target group for AIT/HIIT, especially initially, appears to be small, or more limited than in patients with preserved LV-EF. Studies confirm that many patients cannot meet the targets of high-intensity training, at least at first. This means that in using high-intensity interval training, considerable expenditure is needed for individually-adapted implementation and supervision of training. It appears to be suitable for patients who are more resilient, motivated and able to exert themselves more.
5. In the clinical setting, the postulated time advantage of about 30 min / week is less relevant. High-intensity interval training appears advantageous especially in the context of outpatient CR phase III.
6. (Neutral) one-year data are available only for SMARTEX-HF (for AIT) (9). In general, however, long-term observations which confirm the prognostic role of AIT/HIIT in CHF-HFrEF are missing in all other studies or meta-analyses.
7. HIIT/AIT protocols should be examined with more differentiation in future studies, also with a focus on adherence to the defined protocols/energy expenditure, in order to enable differentiated recommendations for specific patient groups among the CHF-HFrEF patients. This could hypothetically increase the adherence (or further adherence) to physical activity. Especially the training status and comorbidities existing prior to CR must be taken into account.

Conflict of Interest
The authors have no conflict of interest.

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Table 1 – 1st part

Summary of the results of randomized studies in which the effectiveness of interval training, including high-intensity interval training (INT) versus moderate continuous training (MCT) in CHF-HFrEF patients is compared.

STUDY/ AUTHOR	GROUP (N)	AGE (YRS)	MEN (%)	LV-EF (%)	TRAINING MODE	INTENSITY
Meyer et al., 1996 (22)	9	51	100	21	cycle & walking	30s work: 60s at 15W 50% peak work
	9	53	100	22		sedentary control
Willenheimer et al., 1998 (45)	22	64	70	35	cycle	90s work: 30s rest at 80% peak VO_2
	27	64	73	36		sedentary control
Nechwatal et al., 2002 (27)	20	46	95	29	cycle	30s work:60s at 15W 50% peak work
	20	48	90	27	cycle	Cont. 75% peak
	10	49	100	27		sedentary control
Delagradelle et al., 2002 (46)	10	60	100	31	cycle	2min 50% peak VO_2: 2min 75% peak VO_2
	10	56	100	27	cycle & RT	Combined interval and resistance training
Sabelis et al., 2004 (47)	36	57	70	29	cycle	30s work: 60s rest 50% peak work
	25	62	80	26		sedentary control
Dimopoulos et al., 2006 (6)	10	59	90	35	cycle	30s work:30s rest 100% peak work
	14	62	100	31	cycle	Cont. 50% work rate
Roditis et al., 2007 (48)	11	63	91	31	cycle	30s work: 30s rest 100% peak work
	10	61	90	34	cycle	Cont. 50% work rate
Wisloff et al., 2007 (43)	9	77	78	28	treadmill	4min work, 90-95% peak HR, 3min recovery 50-70% peak HR
	9	74	78	33	treadmill	Cont. 75% peak HR
	9	76	67	26		sedentary control
Kemps et al., 2010 (49)	30	62	80	32	cycle	30s work: 60s rest 50% peak work
	18	63	72	33		sedentary control
Nilsson et al., 2010 (50)	39	69	77	30	aerobic	15-18 RPE Borg scale
	39	72	80	31		sedentary control
Tasoulis et al., 2010 (38)	21	53	90	34	cycle	30s work: 60s rest 50% peak work
	25	53	76	36	cycle & RT	Combined interval and reistance training
	11	53	73	<50		sedentary control
Anagnostakou et al., 2011 (2)	14	52	86	36	cycle	30s work: 60s rest 50% peak work
	14	54	79	39	cycle & RT	Combined interval and reistance training
Bouchla et al., 2011 (51)	10	50	90	38	cycle	30s work: 60s rest 50% peak work
	10	57	70	33	cycle & RT	Combined interval and reistance training
Smart et al., 2012 (34)	10	59	80	27	cycle	60 s work:60 s rest 70% peak VO_2
	13	63	100	27	cycle	Cont. 70% work rate
Freyssin et al., 2012 (11)	12	54	50	28	cycle & RT	30s work: 60s rest 80-120% peak work & gym
	14	55	50	31	cycle & treadmill & RT	Contin. at VAT1 & gym
Fu et al., 2013 (12)	14	68	64	28	cycle	3 min work, 80% VO_2peak, 3 min recovery 40% VO_2peak
	13	66	62	31	cycle	Cont. 60% peak VO2
Iellamo et al., 2013 (17)	8	62	100	34	treadmill	4min work, 75-80% HRR, 4min recovery 45-50% HRR
	8	62	100	32	treadmill	Cont. 45-60% HRR
Chrysohoou et al., 2014 (5)	33	63	88	30	cycle	30 s work:30 s rest 100% peak work
	39	56	82	32	cycle	sedentary control
Ellingsen et al., 2016 (9)	77	65	82	29	cycle or treadmill	4 min work, 90–95% peak HR, 3 min recovery 50–70% peak HR
	65	60	81	29	cycle or treadmill	Cont. 60-70% peak HR
	73	60	81	30		sedentary control

Table 1 – 2nd part

CHF-HFrEF=chronic heart failure with reduced ejection fraction; CON=control group; LV-EF=left ventricular ejection fraction; VO_2peak=peak oxygen uptake. Modified from (16, 35).

DURATION (MIN)	FREQUENCY (DAYS/ WEEK)	INTERVENTION LENGTH (WKS)	KCAL/WEEK	MEANΔVO_2PEAK (ML/KG/MIN) VS. SEDENT. CG* OR OTHER INTERVENTION**
25	5	3	217	
				2.30 [0.79, 3.81]*
15 titrated up to 45	2 to 3	16	565	
				1.00 [0.15, 1.85]*
15	6	3	198	
15			198	-0.10 [-1.70, 1.50]**
				1.60 [0.19, 3.01]*
40	3	16	595	
40 plus RT	3			-1.00 [-1.96, -0.04]**
15	4	26	110	
				1.50 [0.48, 2.52]*
40	3	12	393	
40	3			0.30 [-0.72, 1.32]**
40	3	12	330	
40	3			-0.10 [-1.46, 1.26]**
38	3	12	660	
47	3		660	4.10 [2.78, 5.42]**
				5.80 [3.89, 7.71]*
15	3	12	110	
				1.90 [0.33, 3.47]*
50	2	16	NR	NR
40	3	12	277	
40 plus RT	3		NR	-1.50 [-3.24, 0.24]**
				0.80 [-0.24, 1.84]*
40	3	12	135	
40 plus RT	3			-1.10 [-3.08, 0.88]**
40	3	12	138	
40 plus RT	3	16		-1.00 [-3.28, 1.28]**
60	3		467	
30	3		467	1.20 [-1.22, 3.62]**
168 / week	5	12	NR	
360 / week	5		NR	2.70 [-0.06, 5.46]**
30	3	12	NR	
30	3			3.50 [0.35, 6.65]**
32	2 to 5	12	NR	
30-45	2 to 5			0.15 [-3.88, 4.18]**
45	5	12	NR	
				4.00 [NR]*
38	3	12	<660*	
47	3		>660*	-0.40 [-1,70, 0.80] **
				1.40 [0.20, 2.60] *