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(Wissenschaftlicher Vorstand: Prof. Dr. med. Michael Baumann)

Abteilung Bewegung, Präventionsforschung und Krebs

(Leitung: Prof. Dr. rer. nat. Karen Steindorf)

Exercise interventions for breast cancer survivors - Investigations of attendance and of short- and long-term effects on the exercise and physical activity behavior

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Sarah Siri Goldschmidt

aus

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Dekan: Herr Prof. Dr. rer. nat. Michael Boutros

Doktormutter: Frau Prof. Dr. rer. nat. Karen Steindorf

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List of abbreviations

%VO_2max	percentage of the maximal oxygen uptake
%	percent
%HRmax	the percentage maximum heart rate
1-RM	one-repetition maximum
ACS	American Cancer Society
ACSM	American College of Sports Medicine
AICR	American Institute for Cancer Research
AT	aerobic exercise training
BENEFIT	BEwegung bei NEoadjuvanter Chemotherapie zur Verbesserung der FITness (Exercise for breast cancer patients undergoing neoadjuvant chemotherapy)
BMI	body mass index
BRCA	breast cancer genes
CES	cumulative effect size
CG	control group
Chi^2	chi-square test
CI	confidence interval
CIPN	chemotherapy-induced peripheral neurotoxicity
CRFs	case report forms
EORTC-QLQ-BR23	23- item breast cancer specific EORTC module
EORTC-QLQ-C30	30-item European Organization for Research and Treatment of Cancer quality of life questionnaire for cancer patients
FA	fatigue
FES-I	Falls Efficacy Scale-International
HDI	Human Development Index

HR	hormone receptor
IG	intervention group
IGF	insulin-like growth factors
L/min	oxygen uptake in liters
M	mean
MET	metabolic equivalent of task
min	minutes
MSPSS	Multidimensional Scale of Perceived Social Support
MVPA	moderate-to-vigorous physical activity
NACT	neoadjuvant chemotherapy
NCT	National Center for Tumor Diseases
PA	physical activity
PE	physical exercise
PRO	patient-reported outcomes
Q1	first quartile
Q3	third quartile
QoL	quality of life
RCT	randomized controlled trial
RT	resistance exercise training
SAS	Statistical Analysis System
SD	standard deviation
SMD	standardized mean difference
SQUASH	short questionnaire to assess health enhancing physical activity
VO_2max	maximal oxygen uptake
WCRF	World Cancer Research Fund
WHO	World Health Organization

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1 Introduction

1.1 Breast cancer

1.1.1 Breast cancer - Epidemiology

Globally, the number of cancer diagnoses per year rises: Compared to 2018, there were an additional 1.2 million new cancer cases, i.e., a total of 19.3 million people who were newly diagnosed with cancer in 2020 (Bray et al. 2018; Sung et al. 2021). Globally, the five most common types of cancer refer to the female breast (i.e., 11.7 percent (%) of all cancer cases), lung (11.4%), prostate (7.3%), colon (6.0%) and stomach (5.6%) (Sung et al. 2021). Female breast cancer shifted from the second place in 2018 (11.6%) to the first place, accounting with globally 2.2 million cases for the most frequent type of cancer in 2020 (Bray et al. 2018; Sung et al. 2021).

The different frequencies of the cancer entities reveal the assumption that depending on the geographical area, rather the 4-tier Human Development Index (HDI; i.e., a measure for the development of a country) (United Nations Development Programme 2019), as well as its sole socioeconomic development, the exposure to different risk factors may be related to the cancer development, as also the access to the healthcare system, i.e., cancer prevention, screening, diagnosis, and treatment (Lortet-Tieulent et al. 2020; Sung et al. 2021). The incidence of female breast cancer is twice as high in high compared to those in low HDI-countries, but the mortality rates are higher in lower than higher HDI-countries (Lei et al. 2021; Lortet-Tieulent et al. 2020; Sung et al. 2021). These differences suggest to be related to better screening opportunities in higher HDIs that enable early detection of female breast cancer. Better screening opportunities may account for a higher number of female breast cancer cases in high than might be found in low HDI-countries without comparable screening opportunities (Lortet-Tieulent et al. 2020; Sung et al. 2021). Beside the screening opportunities, the genesis as well as the risk factors related to the development of breast cancer play a crucial role.

1.1.2 Breast cancer - Genesis

Although the process of cancer development is not yet fully understood, the tumor genesis described by Hanahan and Weinberg (2000, 2011) and updated by Hanahan (2022), in which they identified 12 hallmarks and characteristics that enable tumor development, is generally acknowledged (Hanahan 2022; Hanahan and Weinberg 2000; Hanahan and Weinberg 2011). The process that leads to the development of cancer is very complex (National Cancer Institute 2021; Harvard Medical School 2011). Due to a change within the cell’s function, the cells grow unrestrictedly and uncontrollable which results in the formation of tissue mass of cells, a tumor (National Cancer Institute 2021; Harvard Medical School 2011). This formation can be either benign (i.e., not cancer) or malignant (i.e., cancer), which is usually differentiated by the growth (proliferation) (National Cancer Institute 2021). Only cancer may invade into and spread to other tissue, whereas benign tumors don´t (National Cancer Institute 2021). The process, in which cancer develops, is called ‘carcinogenesis’ (Harvard Medical School 2011). Every organism consists of a bunch of several different types of cells with different functions that enables the organism’s different functions and, thus, living (Königshoff and Brandenburger 2012; WCRF/AICR 2018). This is enabled by mitosis, an important process that refers to the duplication of one cell into two cells, entailing exact the same information as the original cell (Königshoff and Brandenburger 2012; WCRF/AICR 2018). As this is a very complex process, it is supervised by cyclin-based regulatory proteins and cyclin-dependent kinases (Königshoff and Brandenburger 2012; WCRF/AICR 2018). One of these proteins is the Trp53 protein (formerly p53) that guards the cell cycle and induces apoptosis (cell death) in case of any damage to prevent the further dissemination of defective cells. Thus, Trp53 belongs to the tumor suppressor proteins (Königshoff and Brandenburger 2012). This protein is encrypted on the TP53 tumor suppressor gene (Hainaut et al. 2013). A disruption in the process due to intrinsic and extrinsic factors may promote uncontrollable cell division and/or growth (Königshoff and Brandenburger 2012). The development of cancer may be concluded as the inability of the immune system to identify defective cells and the ability of these cells to evade and manipulate the cell cycle’s functions that shall prevent the development and distribution of defective cells (Hanahan 2022; Hanahan and Weinberg 2000; Hanahan and Weinberg 2011). Additionally, the existing signaling pathways can be manipulated by the defective cells to avoid their death and instead promote their own growth (Hanahan 2022; Hanahan and Weinberg 2000; Hanahan and Weinberg 2011). Thus, the immune system plays a not negligible role in the development of cancer and may be influenced by several factors differentiated in internal factors, including mutations and hormones, and external factors encompassing the lifestyle and the environment, like the exposure to sun or pollution (Campos et al. 2022; Sung et al. 2021). Some specific risk factors are described in more detail in the subsequent section.

1.1.3 Breast cancer - Risk factors

The risk factors of breast cancer development are differentiated into modifiable and non-modifiable factors (Friedenreich et al. 2021; WCRF/AICR 2018; Winters et al. 2017). Non-modifiable risk factors include family history, gene mutations, age, breast density and reproductive patterns like age at menarche and menopause and, to some extent, parity and breastfeeding (Campos et al. 2022; WCRF/AICR 2018). Modifiable factors encompass all factors related to lifestyle choices, i.e., physical activity, sedentary behavior, weight, body composition, diet, alcohol and tobacco consumption (i.e., lifestyle factors) (Lortet-Tieulent et al. 2020; Sung et al. 2021; WCRF/AICR 2018; Winters et al. 2017). The most common risk factors of breast cancer development are thought to be mainly hormone-related determinants, which may be only partly modifiable regarding the intake of hormones for birth control or during menopause (i.e., hormone replacement therapy) (Sung et al. 2021; WCRF/AICR 2018; Winters et al. 2017).

The impact of the individual's lifestyle on the development of breast cancer is complex as it may be directly through the exposition to carcinogenic components (e.g., through food or pollution) or indirectly by altering the biological processes, like the hormone signaling (Avgerinos et al. 2019; WCRF/AICR 2018). Obesity is one prominent risk factor that is generally acknowledged to be related to various alterations of biological processes that facilitate breast cancer growth (Avgerinos et al. 2019). Obesity is related to increased hormonal levels and insulin-like growth factors (IGF), which not only promotes the growth of healthy tissue, but also the development of cancer (Avgerinos et al. 2019). Furthermore, the obesity-related higher amount of fat tissue was observed to increase estrogens which further promotes the growth of breast tissue (Avgerinos et al. 2019). Also, fat tissue promotes inflammatory processes, which alter the body microenvironment that facilitates cancer growth (Avgerinos et al. 2019). The alteration of the body microenvironment may be either directly or indirectly by weakening the gut barrier, altering the intestinal microbiomes, and promoting the production of carcinogenic metabolites (Avgerinos et al. 2019). These changes then facilitate inflammatory processes that promote the production of estrogen, which is related to the overall development and further growth of breast tissue (Avgerinos et al. 2019). As obesity usually develops through a higher intake of energy than is needed by the metabolism, it may be controlled through eating a healthy diet and being regularly physically active (WCRF/AICR 2018).

A healthy lifestyle according to the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) comprises a healthy diet, which is based on the Mediterranean diet that mainly entails fresh fruits, vegetables, plant-based foods, legumes and wholegrains (WCRF/AICR 2018). The consumption of salt-preserved foods, red and processed meat, sugar sweetened beverages, alcohol and tobacco shall be reduced, rather avoided (WCRF/AICR 2018). The findings of tobacco in association with breast cancer were inconsistent, however smoking shall be avoided, due to its association with the development of other cancers (WCRF/AICR 2018). A recent meta-analysis depicted a dose-response relationship between the smoking behavior and breast cancer risk (Scala et al. 2023). The increased risk of developing breast cancer is 7% for former smokers, 8% for current smokers and 9% for ever smokers (Scala et al. 2023). Thereby however, the time since quitting revealed no association with the risk of developing breast cancer (Scala et al. 2023). But, the smoking duration in years was linearly associated with an increased risk of developing breast cancer, i.e., the longer an individual smoked, the higher the risk of developing breast cancer (Scala et al. 2023). Alike, the amount of cigarettes per day was also linearly associated with an increased risk of developing breast cancer (Scala et al. 2023). Similarly, a meta-analysis observed a dose-response relationship between the overall consumption of 20 gram of alcohol and the increase of the relative risk of developing breast cancer of about 22% (Sun et al. 2020).

Thus, the individual's risk of developing breast cancer may be reduced following these recommendations and engage in regular physical activity (displayed in more detail in section 1.2) (Friedenreich and Cust 2008; WCRF/AICR 2018). Furthermore, following these recommendations shall promote the maintenance of a healthy weight, which itself is related to a decreased risk of breast cancer (WCRF/AICR 2018).

It may be difficult to rule out the influence of lifestyle-related risk factors from those associated with the risk of hereditary breast cancer, i.e., women with a mutation in any of the breast cancer genes (BRCA) and those women with a positive family history of breast cancer. A meta-analysis compared the influence of alcohol consumption, smoking behavior, obesity and physical activity behavior in women with a positive family history of breast cancer with women who have a genetic mutation in either BRCA1 or BRCA2 or both (Cohen et al. 2023). The results were mixed, as some modifiable risk factor were observed to have an influence on the breast cancer risk in BRCA1 and/or BRCA2 or women with family history of breast cancer and some did not (Cohen et al. 2023). The mixed findings were attributed to the varying definitions of each of the modifiable risk factors (e.g., classification of former or current smoker or alcohol drinker) (Cohen et al. 2023). Thus, the influence of lifestyle-related modifiable risk factors on the breast cancer risk in women with a BRCA1/2 mutation or family history of breast cancer is not yet fully understood (Cohen et al. 2023). Certainly, 5-10% of all breast cancer cases are attributed to genetic mutation of BRCA1/2 (WCRF/AICR 2018) and about 20% are at least partly attributed to modifiable lifestyle-related risk factors (Armenta-Guirado et al. 2023).

1.1.4 Breast cancer patients and survivors

Due to improvements in screening, diagnostics and therapy, the number of cancer survivors is increasing, with approximately half of all cancer survivors living ≥ 10 years after their cancer diagnosis (Allemani et al. 2018).

The term 'cancer survivor' describes an individual from the time of the cancer diagnosis until death, irrespective of the current treatment status (Denlinger et al. 2014). However, 'cancer survivor' is often interchangeably used with 'cancer patient'. In this thesis, the term cancer patient is used mainly for individuals during or shortly after cancer treatment.

Dependent on the received treatment, many cancer survivors suffer from long-term (i.e., several years after treatment completion) or life-long cancer therapy-related side-effects, e.g., cardiac dysfunction, loss of physical function and fitness, bone density, sleep difficulties, fatigue, pain, neuropathy, menopausal symptoms, cognitive impairment, anxiety or depression that can negatively influence their quality of life (QoL) (Moore 2020; Saunders et al. 2022; Schmidt et al. 2022). In their meta-analysis about QoL in cancer survivors, Firkins and colleagues (2020) observed a significantly reduced QoL between 2 years and up to 26 years after the cancer diagnosis (Firkins et al. 2020). There, QoL of all areas was affected, revealing an overall perceived reduced QoL (global QoL; cumulative effect size (CES)= -0.65, 95%-confidence interval (*CI* [-1.20, -0.10]), the reduced ability to walk, to take the stairs or to dress and to wash oneself (physical health; CES=-0.89, 95% CI [-1.47, -0.32]), difficulties to perform the activities of daily living beyond dressing or washing (role-physical health; CES = − 2.04, 95% CI [− 2.64, -1.44]), worse mental health (CES= -0.87, 95% CI [-1.45, -0.29]), lower energy levels (vitality; CES=-0.59, 95% CI [-0.90, -0.28])) and less participation in social interactions with friends and family (social health, CES = − 0.677, 95% CI [− 1.27, − 0.08]) (Firkins et al. 2020).

Besides the long-lasting side-effects that impair the QoL, cancer survivors have an overall worse QoL, lower physical functioning and higher psychological distress, lower physical, role, emotional, social and cognitive functioning and simultaneously significantly higher levels of insomnia, fatigue and dyspnea (Arndt et al. 2017; Doege et al. 2019; Firkins et al. 2020; Joshy et al. 2020; Schmidt et al. 2022). Further known side-effects are, e.g., lymphedema or sensation disturbances at the operated side due to axillary and breast surgery (Fallowfield and Jenkins 2015; Saunders et al. 2022; Schmitz et al. 2010). Chemotherapy is usually associated with nausea, vomiting, loss of hair, low blood count, issues with the mucous membranes, fatigue, pain, cardiac and cognitive impairments, (long-term) neuropathy, loss of physical function and fitness, impaired wound healing (Fallowfield and Jenkins 2015; National Cancer Institute 2023; Saunders et al. 2022; Schmitz et al. 2010). Radiotherapy may cause similar side-effects than the chemotherapy. Endocrine therapies are related to arthralgias, menopausal like symptoms, worse bone health and increased fat with reduced muscle mass (Fallowfield and Jenkins 2015; Saunders et al. 2022; Schmitz et al. 2010).

Physical activity (PA) may alleviate these effects (Figure 1).

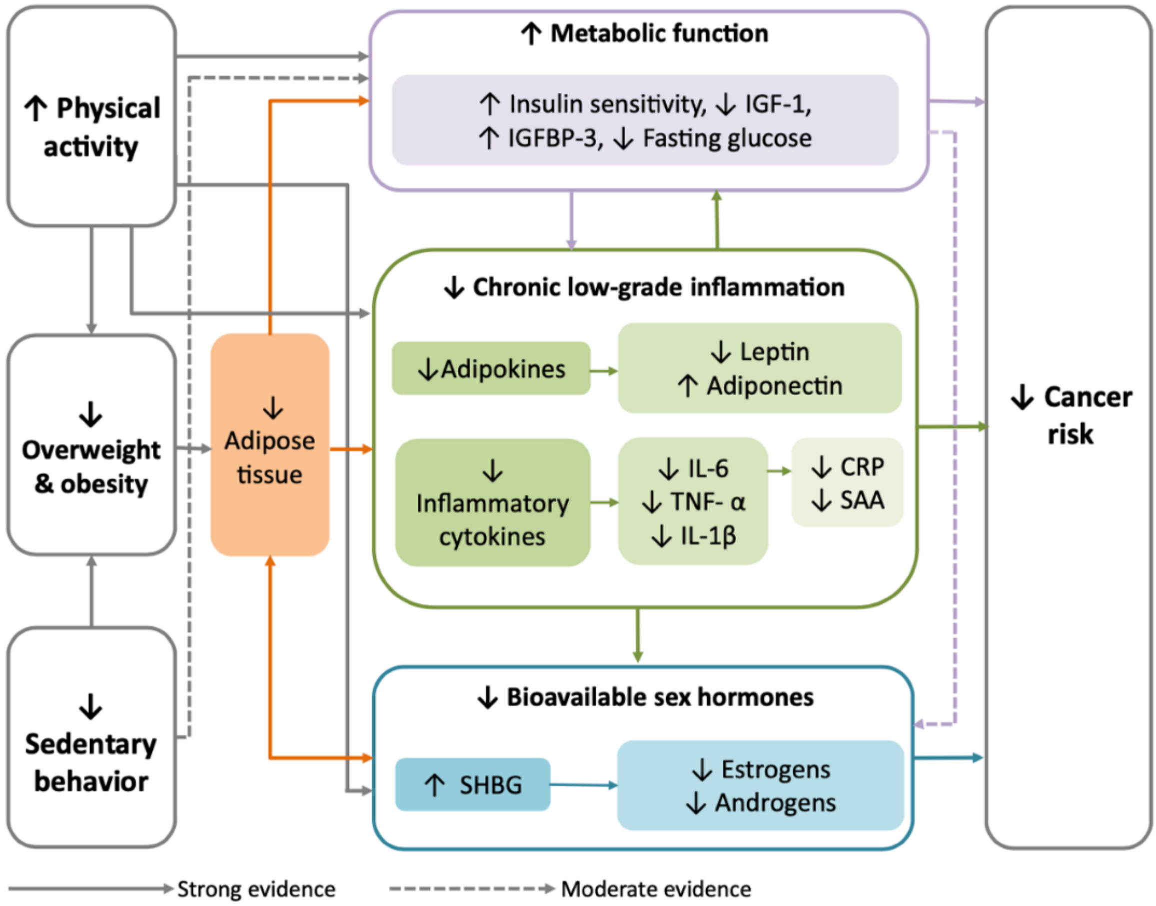


Figure 1: Surmised conjunction between sedentary behavior, physical activity, excess body fat and biological mechanisms (Friedenreich et al. 2021)

The positive influence of PA on the individual's cancer risk is suggested to be direct as well as indirect through the improvement of sedentary, PA and exercise behavior and the obesity-related changes in metabolism and hormonal signaling (Friedenreich et al. 2021). But, according to the World Health Organization (WHO) and the pooled analysis from Guthold and colleagues (2018), one in four adults above the age of 18 years is insufficiently active (Guthold et al. 2018; WHO 2022).

1.2 Physical activity and physical exercise

PA encompasses every type of bodily movement that involves contracting skeletal muscles and, thus, requires energy to perform it (Caspersen et al. 1985). It is further differentiated in the area, where it is performed, i.e., during leisure-time, occupation, household and/or transportation (WHO 2020).Thereof differentiated is physical exercise (PE), which corresponds to the planned and purposeful PA that is performed repetitively, like a work-out, sportive cycling/mountain biking, running or (Nordic) walking with the aim of improving or maintaining physical fitness and/or health (Caspersen et al. 1985; WHO 2020). It usually follows a clear prescription regarding frequency, intensity, time and type (FITT-principles) (Campos et al. 2022). PA and PE are usually quantified according to their intensity, which can be distinguished in relative and absolute intensity (Piepoli et al. 2016). The relative intensity is based on the degree of exertion required by the individual to perform a given activity. This can be expressed via the BORG scale for rating the perceived rate of exertion, but may be also derived from the individual's performance by using the percentage maximum heart rate (%HR_{max}) or from the cardiorespiratory fitness presented as the percentage of the maximal oxygen uptake (%VO_{2max}) (Piepoli et al. 2016). The absolute intensity is based on the energy expenditure per minute that is needed to perform a certain activity (Piepoli et al. 2016). The absolute intensity can be assessed by the oxygen uptake in liters (L/min), but is usually expressed as the metabolic equivalent of task (MET), which is denoted as an oxygen uptake of 3.5 milliliter oxygen per kilogram body weight per minute and corresponds to the metabolic requirement for an adult in rest (Ainsworth et al. 2011; Balke 1960; Piepoli et al. 2016). The intensity of PA is commonly classified as light (1.6-2.9 METs), moderate (3-5.9 METs) and vigorous intensity (≥ 6 METs) (Ainsworth et al. 2011). Everything ≤ 1.5 METs is defined as sedentary behavior (Friedenreich et al. 2021; Tremblay et al. 2017). Unfortunately, this classification does not consider any patient-related variables like sex, age, weight or fitness level, thus, either the usage of relative intensity or a combination of both methods may be more appropriate (Piepoli et al. 2016). The relative intensity can be transformed into absolute intensity (Table 1).

Table 1: Overview of the relationship between different intensities of activities and fitness levels with examples

Perceived intensity	Relative intensity			Absolute intensity	Examples
	%HRmax	%VO2max	BORG	MET	
Very light	< 57	< 37	< 9	1.6-1.9	fishing
Light	57-63	37-45	9-11	2.0-2.9	Walking <4.7 km/h, light household work
Moderate	64-76	46-63	12-13	3.0-5.9	Walking briskly (4.8–6.5 km/h), slow cycling (15 km/h), painting/decorating, vacuuming, gardening (mowing lawn), golf (pulling clubs in trolley), tennis (doubles), ballroom dancing, water aerobics.
Vigorous	77-95	64-90	14-17	> 6.0 – 8.7	Race-walking, jogging or running, bicycling >15 km/h, heavy gardening (continuous digging or hoeing), swimming laps, tennis (single).
Near-maximal to maximal	≥96	≥91	≥18	≥ 8.8	Basketball, drills, practice, rope jumping slow pace (< 100 skips/min)

Table adopted from Piepoli 2016 (Piepoli et al. 2016); American College of Sports Medicine 2011 (Garber et al. 2011) and Ainsworth 2011 (Ainsworth et al. 2011).
BORG - rating of perceived exertion, MET- metabolic equivalent of task, km/h – kilometers per hour, min- minute, %HR_{max}- percentage of maximal heart rate, %VO_{2max}- percentage of maximal oxygen uptake

Not included in these definitions is the overall amount of time that is spent in the respective sedentary and/or PA behavior. The amount of sedentary behavior does not reflect the time spent in PA and vice versa, thus, having high levels of PA does not reflect low levels of sedentary behavior (Tremblay et al. 2017). Based on a regular 24-hour-day, an individual may have a sedentary job, i.e., sitting in an office, but may meet or exceed the general PA recommendations after work (Friedenreich et al. 2021). Vice-versa, an individual may have a work that is physically strenuous and, thus, spends the time off-work sedentary (Friedenreich et al. 2021). Therefore, important is the positive impact of PA on the cancer risk as depicted in Figure 1, which is hypothesized to be achieved through an overall increase in PA and simultaneously reduction of sedentary behavior (Friedenreich et al. 2021).

1.2.1 Physical activity and exercise recommendations

According to the American Cancer Society (ACS, regular PA has been associated with a reduction in the risk of developing pre- and postmenopausal breast cancer (Rock et al. 2020; WHO 2020; Zhang et al. 2020).

Table 2: Recommended physical activity according to the age group (WHO 2020, S. 1-3)

Age group	Type	Duration	Intensity	Frequency
Children and adolescents (5-17 years)	Aerobic	At least 60 minutes	Moderate to vigorous	Daily
	Strength		Muscle-strengthening	3 or more days per week
Adults (18-64 years)	Aerobic	150 - 300 minutes	Moderate	Overall per week
		OR		
		75 – 150 minutes	Vigorous	Overall per week
	Strength		Muscle-strengthening	2 or more days per week
Adults (65 years and above)	Aerobic	150 - 300 minutes	Moderate	Per week
		OR	Vigorous	Per week
		75 – 150 minutes		
	Strength		Muscle-strengthening	2 or more days per week
	Balance			3 or more days per week

Following the recommendations displayed in Table 2, a statistically significant risk reduction for developing breast cancer of approximately 10% to 20% could be observed (Armenta-Guirado et al. 2023; WHO 2020; Zhang et al. 2020). The assumed influence of PA on the breast cancer risk through the interference with the hallmarks of cancer that were identified from Hanahan and Weinberg (2011) is displayed in Table 3.

Table 3: Assumed influence of physical activity and exercise on the hallmarks of cancer (Campos et al. 2022)

Hallmarks of cancer	Influence of physical activity and exercise on the hallmarks of cancer
Sustaining proliferative signaling	Elevation of catecholamines, leading to the deactivation of pathways implicated in proliferation and metastasis
Evading growth suppressors	Elevation of hormone binding globulin, leading to the decrease of circulating estrogen
Resistance of cell death	Reduction of intratumoral lactate, relieving immunosuppression caused by metabolic by-products of the tumor
Blockade of immune checkpoints	Reduction of inflammatory markers, regulating both acute and chronic inflammation
Tumor promoting inflammation	Reduction of macrophage infiltration into tumoral environment, reducing inflammation and trophic functions that benefit tumor progression
Enabling replicative immortality	Signaling to increase cytokine levels, leading to the attraction of natural killer (NK) cells and cytotoxic T cells
Inducing angiogenesis	Increase of body temperature, which promotes vasodilation and shear stress and increase of immune cell access
Activating invasion and metastasis	Reduction of adipocytes and influence in adipocyte and growth factor production, reducing tumor cell formation and metastasis
Dysregulation of cellular energy	Release of myokines in muscle contraction, some of them interleukins involved in immune regulation
Genome instability and mutation	Redirection of energy and substrates, reducing tumor cell metabolism

Additional health benefits for adults (≥ 18 years) can be achieved, if the given PA recommendations of 300 minutes (min) of moderate or 150 min of vigorous activity per week were exceeded (WHO 2020). Simultaneously recommended is the increase in light PA by taking the stairs and the reduction of sedentary behavior (WHO 2020). These recommendations also apply to individuals with chronic non-communicable diseases, including diabetes, cardiac disease and cancer (WHO 2020).

1.2.2 Physical activity and exercise benefits for breast cancer survivors

Exercise interventions revealed improvements in therapy-related side-effects and/or limitations (Campbell et al. 2019; Schmitz et al. 2010), patient reported outcomes (PRO), quality of life or psychological health (Abdin et al. 2019; Campbell et al. 2005; Gokal et al. 2016; Hayes et al. 2013; Lahart et al. 2018; McNeely et al. 2006; Mutrie et al. 2007; Schmitz et al. 2010), well-being (Schmitz et al. 2010), fatigue (Gokal et al. 2016; Hayes et al. 2013; Lahart et al. 2018; McNeely et al. 2006; Mustian et al. 2017; Schmidt et al. 2018; Schmitz et al. 2010), physical fitness and functioning (Abdin et al. 2019; An et al. 2020a; Anderson et al. 2012; Campbell et al. 2005; Courneya et al. 2013; Hayes et al. 2013; Lahart et al. 2018; McNeely et al. 2006; Pinto et al. 2002; Schmitz et al. 2010). Significant improvements of anxiety, depressive symptoms and overall health-related QoL as also fatigue and physical function could be achieved with a training of at least moderate intensity that was performed 2-3 times per week for a period of 12 weeks (Campbell et al. 2019).

1.2.3 Physical activity and exercise behavior of breast cancer survivors

Despite the proven efficacy and safety of exercise during and after chemo- and/or radiotherapy in breast cancer patients and survivors, if it is adapted to the individual’s current health status, respectively the currently experienced side-effects and/or limitations (Campbell et al. 2019; Schmitz et al. 2010; Wolin et al. 2012), breast cancer patients significantly reduce their PA behavior (An et al. 2020a; Andrykowski et al. 2007; Bock et al. 2013; De Groef et al. 2018; Devoogdt et al. 2010; Emery et al. 2009; Littman et al. 2010; Pinto et al. 2002; Schmidt et al. 2017) up to one year after diagnosis, which is mostly congruent with the time of the cancer treatment trajectory (Littman et al. 2010). The highest decrease in PA was observed in breast cancer patients receiving surgery and additional radio- and chemotherapy, who reduced their PA level by half, whereas surgery alone or with additional radiotherapy led to a PA decrease of nearly one quarter (23-24%) (Irwin et al. 2003). Similarly, DeGroef and colleagues (2018) observed a significant decrease in PA after breast surgery (De Groef et al. 2018). Spontaneous improvements in the PA behavior of breast cancer survivors could be observed some months after completing the cancer treatment (De Groef et al. 2018; Devoogdt et al. 2010; Emery et al. 2009; Irwin et al. 2003; Littman et al. 2010; Schmidt et al. 2017), but PA levels remained below those prior to the diagnosis (De Groef et al. 2018; Devoogdt et al. 2010; Littman et al. 2010; Schmidt et al. 2017). Exercise interventions may counteract the reduction and/or termination of PA and exercise during cancer therapy.

1.3 Exercise interventions

Exercise interventions were observed to improve the PA behavior over the duration of the intervention (Bluethmann et al. 2015; Courneya et al. 2007a) and some time after its completion (An et al. 2020b; Bock et al. 2013; Emery et al. 2009; Schmidt et al. 2017; Vallance et al. 2008). But, yet, the effects of exercise interventions on the long-term PA and PE behavior, i.e., the sustainability of the study derived exercise interventions is not yet fully understood. A sustainable effect of an exercise intervention would be the maintenance of the training of the exercise intervention beyond the intervention phase or statistically significant higher PA and PE levels of the intervention group (IG) compared to the control group (CG) in the longer run. Therefore, as a first attempt within the present thesis, a systematic review and meta-analyses about the sustainability of exercise interventions on the longer-term PA and exercise behavior of breast cancer patients was conducted.

Furthermore, it is yet not sufficiently investigated, whether the influence of exercise on the PRO as well as on the longer-term PA and exercise behavior may be further improved through the implementation of a certain type of exercise at a certain time during cancer treatment (Jones and Alfano 2013). Here, previous analyses indicated that exercise during chemotherapy may further improve the medical prognosis by promoting the cytostatically anti-tumoral effects and/or the therapy compliance (Betof et al. 2015; Courneya et al. 2014b). To investigate the influence of exercise during chemotherapy on the PRO, long-term PA and PE behavior, therapy compliance and/or tumor characteristics, the neoadjuvant chemotherapy is the best suitable environment. For this purpose and to contribute to the current body of knowledge, the BENEFIT study, a 3-arm randomized controlled exercise intervention study in breast cancer patients undergoing neoadjuvant chemotherapy was conducted. The neoadjuvant chemotherapy setting reveals the ability to investigate the influence of exercise on the tumor size and chemotherapy efficacy.

1.3.1 Adherence to and attendance at exercise interventions

There is convincing evidence that various significant health benefits may be obtained with a training that is performed 2-3 times a week of at least moderate intensity for a duration of 12 weeks (Campbell et al. 2019). Yet, while the prescribed type, frequency, duration, and intensity of an intervention is of relevance, the patients' adherence to it is also important. The term adherence is defined as following and performing the respective instructions, prescriptions and recommendations as they are provided (Sabaté et al. 2001; WHO 2003). The scope to which the patients follow, i.e., adhere, to these given instructions may have an influence on the intervention efficacy and the patients’ health (Kampshoff et al. 2014; Markes et al. 2006; Sabaté et al. 2001; WHO 2003). Yet, there is no gold standard to measure adherence. But, there are different approaches encompassing the amount of exercise sessions that were performed as described, with regard to the FITT-principles (i.e., frequency, intensity, time, type of the prescribed exercise), the mean minutes of exercise, the number of steps per week or the weekly set exercise goals (Courneya et al. 2014a; Courneya et al. 2008b; Daley et al. 2007b; Foucaut et al. 2019; Hawley-Hague et al. 2016; Hornsby et al. 2014; Husebø et al. 2013; Kirkham et al. 2020; Kirkham et al. 2018; Lund et al. 2019; Markes et al. 2006; Mazzoni et al. 2021; Ormel et al. 2018; Rogers et al. 2015; Schlüter et al. 2022; Schmidt et al. 2017; Turner et al. 2018; van Waart et al. 2020; Witlox et al. 2019). The numbered variety of the different used approaches reveals the complexity of the assessment of adherence to an exercise intervention. The chemotherapy resembles an additional difficult situation to assess the adherence to an exercise intervention, because of the required frequent adjustments of the training prescriptions that may be necessary according to the side-effects of the chemotherapy and the therewith related limitations and health impairments. Therefore, as a simpler approach, the overall attendance at the exercise sessions is commonly investigated as a surrogate measure. This assumption is based on a review, which observed that the majority of included studies defined adherence as attendance or the percentage of attendance records (i.e., attended classes or sessions) (Hawley-Hague et al. 2016).

The term attendance is defined as performing any kind of training irrespective of the predefined exercise prescriptions regarding intensity or duration (Hawley-Hague et al. 2014). The attendance is calculated as the percentage of the performed training units of those, which were previously prescribed (Hornsby et al. 2014; Kirkham et al. 2018; Mazzoni et al. 2021). The existing literature most often investigated the attendance instead of the adherence to the exercise prescriptions (Hawley-Hague et al. 2016).

However, a high attendance is necessary to improve the desired outcome and is, therefore, an important influenceable aspect of intervention adherence. It is susceptible to several treatment- and/or patient-related determinants, including but not limited to socio-demographic factors, age, family status, related costs, travel distance or the overall access to the healthcare system (Courneya et al. 2014a; Courneya et al. 2008b; Daley et al. 2007b; Foucaut et al. 2019; Hornsby et al. 2014; Husebø et al. 2013; Kirkham et al. 2018; Lund et al. 2019; Ormel et al. 2018; Witlox et al. 2019; WHO 2003, S. 3 and lines 135ff). The attendance rate of breast cancer patients to exercise sessions ranges in the current literature between 41% up to 83% (Courneya et al. 2008b; Courneya et al. 2007b; Foucaut et al. 2019; Hornsby et al. 2014; Mazzoni et al. 2021; Schmidt et al. 2017; Witlox et al. 2019). Supervised exercise sessions had a slightly better attendance than the home-based training (Husebø et al. 2013; Lund et al. 2019; Mazzoni et al. 2021; Turner et al. 2018). The primary reason of unattended training sessions in adjuvant breast cancer patients were therapy-related side-effects, followed by life-related (like work or family care), motivational reasons and a lack of time (Courneya et al.

2008b; Foucaut et al. 2019; Hornsby et al. 2014; Kirkham et al. 2018; van Waart et al. 2020). Further determining factors were the group assignment within the study setting, the travel distance, socio-demographic (e.g., family status , children, support), physiological and physical (e.g., fitness, VO_2 peak, age, body mass index (BMI)), behavioral and psychological determinants (e.g., self-efficacy, exercise motivation and history, smoking and alcohol status, mood), with mixed and partly contrary findings across the literature for some of the factors (Courneya et al. 2014a; Daley et al. 2007b; Husebø et al. 2013; Lund et al. 2019; Ormel et al. 2018; Witlox et al. 2019). The major barriers for exercise attendance after completing the cancer treatment were work- and vacation-related, accounting for 60% of all unattended sessions (Kirkham et al. 2018). Similar tendency regarding differences in the timing of an intervention could be observed in another study, in which patients who received the exercise intervention at the beginning of their chemotherapy were better in maintaining the weekly frequency of the training than those receiving the intervention following the cancer treatment completion (Chou et al. 2012). Possible reasons could be the patient's impaired health (Browall et al. 2018; Chou et al. 2012; Courneya et al. 2008a) during cancer treatment, which might reduce the attendance at the training intervention (Browall et al. 2018; Courneya et al. 2008b).

Yet, considering exercise interventions during chemotherapy, data on attendance patterns and influencing factors is still scarce and inconclusive. To evaluate the influence of therapy-related side-effects on the exercise attendance, it may be meaningful to assess these, as well as all other treatment-susceptible factors during the treatment phase. However, previous studies usually considered those factors assessed either before or after finishing the cancer treatment (Courneya et al. 2014a; Daley et al. 2007b; Husebø et al. 2013; Lund et al. 2019; Witlox et al. 2019). Therefore, the second aim of the present thesis was the investigation of the patterns and possible influencing factors of attendance at exercise interventions of breast cancer patients during neoadjuvant chemotherapy.

1.3.2 Training maintenance after the end of exercise interventions

In addition to the attendance at exercise interventions, participants need to continue exercising beyond the study intervention in order to maintain the exercise-related health benefits (An et al. 2020a). The investigation of the training maintenance after the exercise interventions of the BENEFIT study and the subjective reasons of the patients and possible objective influencing factors were investigated as another component in the present thesis.

The maintenance of the training after completing the study exercise intervention was reported to range from 17% to 80% (An et al. 2020b; Courneya et al. 2009; Hayes et al. 2018; Husebø et al. 2014; Mazzoni et al. 2021; Møller et al. 2020; Pinto et al. 2013; Rogers et al. 2015; Schmidt et al. 2017; Witlox et al. 2018). Possible influencing factors encompass socio-demographics (e.g., age, BMI, civil status and education), PRO (e.g., fatigue, anxiety, depression, pain), PA and exercise behavior prior to the cancer therapy, physical fitness post-intervention, type of chemotherapy and surgery (An et al. 2020a; Courneya et al. 2009; Kampshoff et al. 2014; Mutrie et al. 2012; Schmidt et al. 2017). The impact of these factors varied between the studies and was partly contradictory.

So far, various further factors like the patients' personal reasons for (dis-) continuing the training of the study exercise intervention after its completion are understudied in previously conducted studies. This may be of profound interest, as the exercise training within the setting of a study is usually free of charge and the patients receive intensive encouragement to follow the exercise protocol. Thereby, the extensive supervision may provide a safe setting to follow the exercise prescription as the patients do not need to fear to harm themselves. Additionally, the time may play a non-negotiable role, as the interventions are often conducted during the cancer treatment, when the cancer patients are mostly on paid sick leave. Thus, time constraints, family and/or work duties, the costs for a gym membership to continue the training and also the distance to the training facility may be possible further influencing factors that need to be considered to improve the exercise maintenance of breast cancer patients who completed an exercise intervention study (Browall et al. 2018).

1.4 Aims and research questions

As elaborated above, the literature is still inconclusive regarding the effects of exercise interventions on the longer-term PA and PE behavior. Furthermore, there are open questions regarding the patterns and determinants of attendance at exercise interventions during chemotherapy as well as training maintenance after the end of the interventions.

Therefore, the aims of this thesis were:

1. To perform a systematic review and meta-analyses of the current evidence regarding the effects of exercise interventions on medium- and long-term PA behavior in breast cancer patients under consideration of different types and assessments of PA (e.g., total or moderate-to-vigorous PA, subjective versus objective assessment) and different intervention characteristics (e.g., supervised vs. unsupervised training; training during or after cancer therapy; aerobic or resistance training).
2. To investigate the attendance of breast cancer patients at randomized exercise interventions during neoadjuvant chemotherapy and possible determining factors in the BENEFIT study.
3. To investigate the training maintenance beyond the end of the exercise interventions with regard to the proportion of patients maintaining their exercise intervention, the duration, the reasons for (non-) maintenance and possible influencing factors in the BENEFIT study.

The results shall improve the current body of evidence to enable adjustments in the exercise oncology setting for improving the attendance at training offers during chemotherapy as well as their sustainability with respect to longer-term health benefits.

2 Material and Methods

Some of the subsequently presented methods and analyses may correspond to the publications: (Goldschmidt et al. 2024a; Goldschmidt et al. 2024b; Goldschmidt et al. 2022).

2.1 Systematic review and meta-analyses

To assess the influence of an exercise intervention study on the medium and longer-term PA behavior of breast cancer patients after completing the intervention phase (aim 1 of the thesis), a literature-based systematic review and meta-analyses were performed. The review and meta-analyses considered (1) different types of PA (i.e., total PA, MVPA), (2) the mode of PA assessment (i.e., subjective or objective) and (3) different intervention characteristics (i.e., supervised vs. unsupervised training; training during or after cancer therapy; aerobic or resistance training).

To identify eligible studies, a systematic search according to the Preferred Reporting of Systematic Reviews and Meta-analysis (PRISMA) guidelines was conducted in the databases Cochrane, Embase, PubMed, and Web of Science. Included in the review were randomized controlled exercise intervention studies that were published until January 2022, written in German or English, and provided either an aerobic or resistance exercise intervention, a combination of both, or a walking intervention to breast cancer patients. Studies were eligible, if the intervention was of at least moderate intensity and had a minimum duration of four weeks. Further, regarding the outcome, the exercise intervention studies had to have assessed PA behavior at baseline and at least at one follow-up assessment more than eight weeks after the exercise intervention in the IG and CG. No restrictions were defined concerning the tumor or treatment stage nor the type of CG. The search strategies are presented in Annex 8.1.1.

From each eligible randomized controlled intervention trial (RCT), the characteristics of the study population (e.g., mean age, stage of treatment), characteristics of the intervention (i.e., aerobic exercise, resistance training, combination of both, walking intervention) and CG (e.g., usual care, waitlist control, stretching control), intervention setting (i.e., supervised or unsupervised) and the PA assessment method (i.e., subjective or objective) were extracted. Additionally, the characteristics of the intervention (i.e., type: aerobic or resistance training or a combination of both or a walking intervention, setting: supervised or unsupervised home-based, or a combination, frequency: scheduled number of training sessions per week), length of sessions, duration of the intervention period, the number of follow-up assessments, the follow-up time in months after the end of the intervention, the type and unit of the PA variable (e.g., total PA in MET*hours/week, vigorous PA in min/week) were documented and stratified into the subgroups considering intervention setting and PA assessment separately for each, total PA and MVPA.

If any information was missing, an author of the respective publication was contacted.

For each study, the methodological quality was assessed according to the Cochrane Collaboration's recommended criteria for risk of bias (Higgins et al. 2021).Two researchers independently performed the scoring of the risk of bias and divergent scoring was discussed and resolved together with a third reviewer. A high risk of detection bias is suggested if the outcome PA was self-reported. Studies with higher risk of bias (i.e., three or more high risk of bias categories) were excluded in sensitivity analyses to assess their influence on the results (Schmucker et al. 2017).

The publication bias was assessed using funnel plots to visually assess small study effects in the meta-analyses. Due to the asymmetry of the funnel plot, the Egger's test should be performed (Higgins and Green, 2011), which was however not possible due to the small sample size in the subgroups considered in the meta-analyses. Instead, the comprehensive Meta-Analysis Prediction intervals software (www.Meta-Analysis.com/Prediction) was used to assess the heterogeneity between the groups. Therewith, the range of true effects for 95% of a comparable population can be presented (Borenstein et al. 2017).

2.2 The BENEFIT study

Some of the subsequently presented information may correspond to the publication: Kreutz et al. 2020 and the related doctoral thesis: Kreutz 2020.

The BENEFIT study (BEwegung bei NEoadjuvanter Chemotherapie zur Verbesserung der FITness; Exercise for breast cancer patients undergoing neoadjuvant chemotherapy) is a 3-arm randomized controlled exercise intervention trial in patients with breast cancer undergoing neoadjuvant chemotherapy (clincialtrials.gov NCT02999074) that was conducted as a cooperation between the German Cancer Research Center, the University Medical Hospital of Heidelberg and the University Medical Center in Utrecht (The Netherlands). After the approval of the ethics committee of the Medical Faculty of the University Heidelberg (S-678/2015) in 2015, the recruitment began in January 2016 until its completion end of October 2022. The vast majority of patients were recruited in Heidelberg with a few further patients from the University Medical Center in Utrecht.

Patterns and potentially influencing factors of attendance at exercise interventions and maintenance of the training after end of the interventions (aims 2 and 3 of the thesis) were investigated within the ongoing randomized controlled BENEFIT trial. The BENEFIT study is conducted by the Division of Physical Activity, Prevention and Cancer [DKFZ] together with the Working Group Exercise Oncology of the Division of Medical Oncology [UKHD]. During my PhD project, I recruited the participants and performed or coordinated the study assessments. For this PhD project, the BENEFIT assessments were extended by three self-developed questionnaires and one follow-up assessment.

Primary objective of the BENEFIT study is the investigation of the impact of either an aerobic exercise training (AT) or a machine-based resistance exercise training (RT) compared to no training (usual care CG) during neoadjuvant chemotherapy (NACT) on the tumor (i.e., change in tumor size) in breast cancer patients. Secondary outcome measures comprise PRO (quality of life, fatigue, depression, anxiety, sleep quality), physical fitness and performance, cognitive performance, objective sleep quality and efficiency using the motion sensor ActiGraph wGT3X-BT (ActiGraph, Pensacola, USA), selected clinical biomarkers of blood and urine, and the effect of the interventions on the compliance and tolerance to the chemotherapy.

2.2.1 Study design

The study assessments were conducted prior to the start of chemotherapy (T0; baseline, i.e., prior to the randomization and start of intervention), 9 weeks after the start of the chemotherapy (T1), after completing the chemotherapy and prior to the surgery (T2), 6 months (T3), 12 months (T4) and ≥24 months (T5) after breast surgery (Figure 2). The T5 assessment was only added in 2021 to investigate the exercise maintenance and, thus, encompasses a range of 24 to about 60 months after surgery.

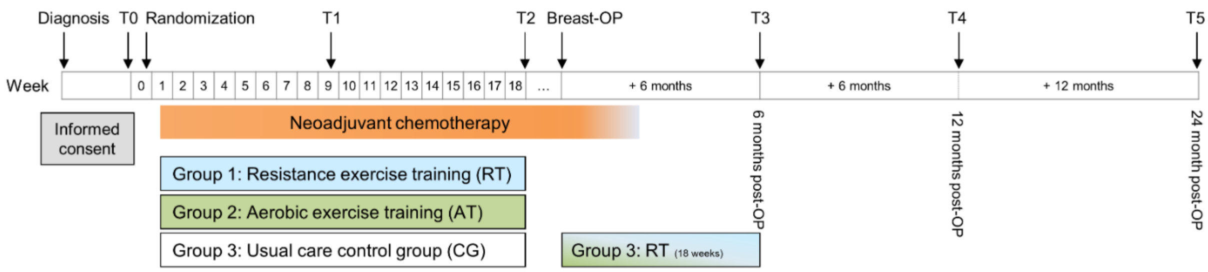


Figure 2: Adopted BENEFIT study scheme

The schedule for all study assessments is presented in Table 4.

Table 4: Adopted timetable for the BENEFIT study assessments

	T0	T1	T2	T3	T4	T5
	Prior to neoadjuvant chemo-therapy and to intervention	Week 9	Week 19 / end of chemo-therapy (before breast surgery)	6 months after breast surgery	12 months after breast surgery	24 months after breast surgery
Socio-demographics	X					
Medical history	X					
Concomitant medication (Log-form)	X		X	X		
Physical activity questionnaire	X		X	X	X	X
Fatigue (Fatigue Assessment Questionnaire and EORTC-FA13/-FA12)	X	X	X	X	X	X
Quality of life (EORTC-QLQ-C30/BR23/CIPN20)	X	X	X	X	X	X
Depression and anxiety score (PHQ-4)	X	X	X	X	X	X
Cognitive functions	X		X	X		
Falls	X		X	X	X	
Sleep questionnaire (PSQI)	X	X	X	X	X	X
Social support (MSPSS)	X		X	X	X	
Work and social life					X	
Weight, BMI, waist, hip	X		X	X		X***
Cardiopulmonary exercise testing (Spiroergometry)	X		X	X		
Muscle capacity (IsoMed)	X		X	X		
Blood and urine sample	X		X	X		
Accelerometry	X		X	X		
Muscle biopsy (optional)	X		X	(X)		
Cardiac biomarkers (optional)	At each CTx admission					

Table 4 (continued)

	T0	T1	T2	T3	T4	T5
	Prior to neoadjuvant chemo-therapy and to intervention	Week 9	Week 19 / end of chemo-therapy (before breast surgery)	6 months after breast surgery	12 months after breast surgery	24 months after breast surgery
Clinical, pathologic, lab parameters	Taken from clinical routine data					
Training adherence	At each training session					
Safety variables	At each training session					
Training evaluation*						
Training continuation**			X	X		
Impact on PA				X	X	X
Current oncological treatment status					X	X
Burdens and support						X
General questions regarding psychological health						X
Post traumatic growth inventory (PTGI)						X

BMI- Body mass index; EORTC-QLQ-C30 - 30-item European Organization for Research and Treatment of Cancer quality of life questionnaire for cancer patients; EORTC-QLQ-BR23 - 23- item breast cancer specific EORTC module; EORTC-QLQ-CIPN – EORTC module to investigate chemotherapy-induced peripheral neurotoxicity; EORTC-QLQ-FA12/13 – EORTC module for fatigue; FAQ - Fatigue Assessment Questionnaire; MSPSS- Multidimensional Scale of Perceived Support; PHQ-4 - Patient Health Questionnaire 4; PSQI – Pittsburgh sleep quality index;
**T2: AT+RT, T3: CG; **starting at T3: AT+RT, starting at T4: CG; ***Patient declaration*

2.2.2 Study population

Eligible were all female patients with breast cancer, who were at least 18 years of age with a BMI of ≥18 kg/m^2, sufficient German language skills, a histologically confirmed primary diagnosed carcinoma of the breast (or a relapse that was not treated within the last two years) with a known hormone receptor (HR) and Her2 status, who were scheduled for (but not yet started) neoadjuvant chemotherapy. Participants should further be willing to train biweekly under the supervision and guidance of experienced exercise and fitness trainers in one of the exercise facilities embedded in the network 'OnkoAktiv' (cooperation partner) and to participate in all study assessments. All breast cancer patients with a physiological or mental condition that may impede the participation at the study training program and/or assessments or those, who already participated in a regular progressive aerobic and/or resistance exercise program (at least 2 x 1 hour per week) were not eligible for the study and, thus, not included. All participants provided informed consent.

2.2.3 Randomization

All included patients, who completed the baseline study assessments, were randomly assigned 1:1:1 to AT or RT over the course of their neoadjuvant chemotherapy or to RT after their breast surgery (CG). The randomization process was based on a blocked randomization, stratified by the relevant prognostic factors for tumor size and the tumor type (HR-; HR+ and HER2+, HR+ and HER2-) using a computerized random number generator. The allocation was performed by a biometrician without any involvement in the patient recruitment and the study personnel did not have access or influence on the patient´s randomization.

2.2.4 Interventions

Both exercise training regimens were conducted according to the exercise guidelines for cancer survivors of the American College of Sports Medicine (ACSM) (Schmitz et al. 2010). Twice weekly, the participants performed a supervised exercise intervention in a public gym or training facility, where other individuals were also exercising. The patients performed their exercise on their own, but oncology-certified trainers were always on site to supervise a correct movement execution and answer potential questions.

2.2.4.1 Aerobic exercise intervention

The patients who were randomized to AT usually performed it on a cycle ergometer, but could have also chosen between other aerobic-based machines like a treadmill, rowing machine, elliptical trainer or alike. However, this was only done in single cases. The exercise program consisted of two phases: The participants began with a supervised 6-week continuous training at 60% of their maximal oxygen uptake (VO_2max) for 15-30 minutes per training session, progressing to 70% VO_2max for 30-60 minutes per training session. From the 7^{th} week onwards, an interval training consisting of four intervals at 75-85% VO_2max with a duration of four minutes and responsively a three-minute recreational interval at 60% VO_2max was performed.

2.2.4.2 Resistance exercise intervention

The resistance training consisted of a machine-based strength training comprising all major upper and lower muscle groups (leg press, leg extension, leg curl, seated row, latissimus pull down, shoulder internal and external rotation, butterfly, and butterfly reverse). Every exercise consisted of three sets with 8 to 12 repetitions per set with a resting time of one minute between the sets and a weight equal to 60-80% of the participants one-repetition maximum (1-RM, that was performed after two familiarization sessions) (American College of Sports Medicine 2009; Brzycki 1993; Chodzko-Zajko et al. 2009; Schmitz et al. 2010).

The 1-RM was performed at every resistance machine according to the Brzycki-method (Brzycki 1993) in the third and last exercise session. The third exercise session was used to enable the patients to get used to the machines and, thus, avoid learning effects, whereas the 1-RM in the last exercise session showed the patient’s current strength compared to that in the third session.

If the aim of three sets with 12 repetitions in three consecutive exercise sessions was successfully accomplished, the weight was increased to the next weight, at least by 5%. Vice versa, if the patient was not able to move the weight at the respective machine the trainer reduced the weight by 5%.

2.2.4.3 Training of the control group

The participants who were randomized to CG, i.e., to the resistance exercise intervention after their breast surgery, did not receive any intervention over the course of the neoadjuvant chemotherapy. However, they were offered the same training as the RT group about 6 to 8 weeks after their breast surgery. The training could only be started with medical clearance to ensure a safe training.

2.2.4.4 Home-based training

Additionally, the patients of the AT and RT groups were asked to perform one unsupervised exercise session of about 15-minute at home according to their randomization. The participants in the AT group should conduct aerobic exercises such as (Nordic) walking or cycling or any other aerobic exercise of their choice with an intensity that was somewhat strenuous (value between 12 to 14 on the BORG scale for rating perceived exertion). Alike, the participants of the RT group performed an approximately 15-minute unsupervised exercise session at home, after an initial 5-minute warm-up. The exercise catalogue was self-developed by the study team and encompassed primarily resistance exercises for the upper extremity, of which three different exercises per week should be chosen. For each exercise, two to three levels of intensity were provided to allow the patient to choose which intensity suits her most and allow progression with improving performance. The exercise and intensity level were supposed to be strenuous (value between 14 to 16 on the BORG scale for rating perceived exertion).

2.3 Measures

To investigate the objectives that relate to the BENEFIT study, items of self-developed and standardized validated questionnaires that assess the PRO and socio-demographic factors were used. Thus, the herein reported data are all self-reported.

2.3.1 Assessment of attendance at the exercise interventions

Exercise attendance was measured with case report forms (CRFs) documented by the patient and a list of signatures maintained by the training facility to reduce the risk of overreporting.

Missing sessions were documented along with the date and respective reasons.

2.3.1.1 Attendance at AT

At the training facilities patients who were randomized to AT reported the start and stop time of the exercise, chose the continued or the interval training according to the study protocol and, therefore, reported the duration of the training or the amount of high and low intensity intervals they performed on which type of gym machine (i.e., cycle ergometer, rowing machine, treadmill, elliptical trainer or other) along with the performance level (Watt) and heart rate.

At home, the AT-patients were asked to record the type of activity (i.e., walking, Nordic walking, running, cycling, swimming or other), the duration in minutes and provide their exertion on the BORG scale for rating perceived exertion.

2.3.1.2 Attendance at RT

At the training facilities, the patients that were randomized into the RT- or CG-group reported the training weight, the number of sets and repetitions performed for every set at every resistance machine.

At home, similar CRFs were completed. The patients documented the number of the three chosen exercises, the performed sets and repetitions, the perceived rate of exertion and the overall duration of the exercise session.

2.3.1.3 Individual exercise attendance

The here reported exercise sessions were used to calculate the overall exercise attendance by dividing the attended through the prescribed training sessions and thereafter multiplied by hundred to get the attendance rate in percent. Per week, two exercise sessions were prescribed for the duration of the intervention. The duration of the intervention was based on the dates prespecified in the study protocol, i.e., the first training session shall be within 7 days after the first chemotherapy administration for AT and RT and should be performed until the post-intervention assessment, i.e., 14 days after the last chemotherapy admission. As the duration of the chemotherapy and, therefore, the duration of the intervention may vary between the patients, the exercise attendance was individually calculated by using the following formula:

Prescribed exercise sessions= ((T2 - date of the first training)/7) *2.

The difference of the two dates reveals the training period in days, which is then divided by seven to receive the training period in weeks and simultaneously reveals the amount of training sessions the patients are supposed to perform at home. This number must be multiplied with two to receive the number of prescribed exercise session in the training facility.

If the patient began the training after the prespecified time range of seven days after the first chemotherapy due to external reasons (e.g., the placement into the training facility took longer or the training facility did not have time) then the aforementioned formula was used too. If the patient could have started, but didn´t, then the following formula was used:

Prescribed exercise sessions= ((T2 – (start of chemotherapy + 7 days))/7) *2.

If the date or the whole T2 assessment couldn´t be performed, due to whatever reasons, then the following formula was used:

T2= (end of chemotherapy + 14 days).

If the training could be started as described in the study protocol or the begin of the training was not within the control of the patient:

Prescribed exercise sessions= (((date of the last chemotherapy + 14 days) - date of the first training)/7) *2

and if the training was not started as intended, but could have been:

Prescribed exercise sessions= (((date of the last chemotherapy + 14 days) – (start of chemotherapy + 7 days))/7) *2.

The CG-patients were supposed to begin their training about six to eight weeks after their surgery depending on the medical clearance and exercised until T3 (6 months after the breast surgery). Thus, the formula to calculate the prescribed exercise sessions is alike the RT and AT formula: If the first training was performed within eight weeks after the surgery, this date was subtracted of the T3-assessment date and divided by seven to receive the training period in weeks and the amount of training sessions for the training at home and was thereafter multiplied with two to receive the number of prescribed exercise session in the training facility:

Prescribed exercise sessions= ((T3 - date of the first training)/7) *2.

If the patient started the training after this range due to external reasons (e.g., not having the medical clearance or the placement into the training facility took longer or the training facility had no time) then this formula was used too. Otherwise, the prescribed exercise sessions were calculated according to the following formula:

Prescribed exercise sessions= ((T3 – (date of breast surgery + 56 days))/7) *2.

If the date was missing and could not be gotten out or the whole T3 assessment could not be performed due to whatever reasons, then the following formula was used:

T3= (date of breast surgery +180 days).

If the patient started as expected or could not start as suggested due to external reasons:

Prescribed exercise sessions= (((date of breast surgery +180 days) - date of the first training)/7) *2

and if the patient could but did not start as suggested:

Prescribed exercise sessions= (((date of breast surgery +180 days) – (date of breast surgery + 56 days))/7) *2.

Using these formulas, the number of prescribed training sessions could be calculated for each patient individually.

Subsequently, the number of prescribed exercise sessions was divided by the amount of performed exercise sessions for each patient.

2.3.1.4 Group-wise attendance per week of training

To compare the attendance between the groups, the number of performed exercise sessions per patient per week within the randomized group was summed up and divided through the expected number of exercise sessions in the respective week. This was then multiplied with hundred to receive the attendance rate per group per week in percent.

2.3.2 Assessment of training maintenance after the end of exercise interventions

To investigate the training maintenance of the BENEFIT exercise interventions and possible related determinants, three questionnaires were developed: ‘Training continuation, ‘Training assessment’ and ‘Impact on PA’. Further possible related determinants were investigated using items of self-developed and standardized validated questionnaires that assess the PRO and socio-demographic factors. Thus, the herein reported data are all self-reported.

2.3.2.1 Questionnaire for the training continuation

Exercise maintenance was defined as the continuation of the training received in the randomized exercise intervention after the study intervention phase at the same or another gym. It was assessed with a self-developed questionnaire asking the survivor first, whether she was still continuing the training, or if not, for how long she had continued the training after the end of intervention (Annex 8.2.1). Participants were asked to complete this questionnaire at all post-intervention follow-up assessments, thus, 6 months (T3), 12 months (T4) and 24 months (T5) after the breast surgery. Subsequently, the patients were asked to indicate their top three (i.e., main, second and third most important) reasons for (not) maintaining the study exercise program based on a predefined list of possible reasons. This list entailed generally acknowledged reasons due to which a healthy adult from the general population would (not) exercise, like time constraints, costs, enjoyment, or well-being. Further other reasons could be reported as free-text that were then grouped together like ‘health issues’ or ‘Corona’ or alike.

2.3.2.2 Questionnaire for the training evaluation

The ‘Training evaluation’ questionnaire was developed to assess the patient’s perception and evaluation of the exercise program (Annex 8.2.2). For this purpose, the patient was asked to answer the following three questions:

First, the patient should indicate which training she had preferred prior to the randomization, with the following options: ‘AT during NACT’, ‘RT during NACT’, ‘generally exercise during NACT’, ‘RT after surgery’ or ‘no preference’. Together with the actual randomization, the answers from this question formed a new variable that was distinguished into having or not having received the indicated preference. Thereafter, the patients should rate the randomized exercise program on a 5-point Likert scale to determine how much they liked their training: 1 = ‘very poor’, 2 = ‘poor’, 3 = ‘OK, 4 = ‘good’, 5 = ‘very good’. Lastly, the third question consisted of twelve prespecified phrases in which the patients were asked to indicate how they felt about various aspects of their exercise program based on a 5-point Likert scale: 1 = ‘extremely negative’, 2 = ‘negative’, 3 = ‘neither negative nor positive’, 4 = ‘very positive’, 5 = ‘extremely positive’.

2.3.3 Assessment of patient characteristics and patient-reported outcomes

2.3.3.1 Socio-demographics

Socio-demographic factors were assessed with a self-developed questionnaire that was already used in previous studies of the Division and entails the marital status (married, divorced, living with or without a partner, being widowed, being single or no declaration), having children (overall and below the age of 18 years, the number of children), number of cohabitants, the highest educational level (no degree, secondary school qualification, general certificate of secondary education, college degree, A-level, other form of graduation, no declaration), highest professional education (no professional training, currently in professional training, industrial training, commercial school, technical school, degree of a university of applied sciences, university degree, another form of polytechnic degree, no declaration), work status (currently working, currently not working).

This questionnaire also entailed the question, whether patients already had experience with strength training, which type of it and when it was performed lastly.

The BMI was calculated from the measured height and weight at the baseline study visit. The weight was measured again at the study visits T2 and T3.

2.3.3.2 Self-reported physical activity and physical exercise behavior

To gather the PA and PE behavior prior to and throughout the study, the participants were asked to indicate the amount of PE (i.e., overall amount of sports) that they performed in their youth (type of exercise, at which age they started and quit, the amount in hours per week and if it was competitive) as well as the amount of walking (at least 20 minutes at a time), cycling and sports within the 12 months prior to the study entry, during the study intervention phase and at all follow-up assessments using questions adopted from the short questionnaire to assess health enhancing physical activity (SQUASH) (Wendel-Vos et al. 2003). For each category, the patients were asked to report the frequency (days per week or month and number of active weeks or months), duration (minutes per day) and intensity (low, moderate, partially vigorous, mostly vigorous) of the activity they engaged in. Additionally, the circumstances in which the exercise was performed were assessed, i.e., alone, with someone else or in a group, at home, in a certain training facility or club. The patients were instructed not to include their intervention program in this information. In case of uncertainty this was clarified directly with the patient and if the intervention program was included, the certain amount of exercise was excluded in the analyses. This enabled comparisons of the PA behavior at all time-points and between the three groups.

At study entry, the experience with strength training was assessed as having experience (yes/no), in a weight room of a gym, with dumbbells or machines or the opportunity to write an answer in the response category ‘other’.

To compare the PA data, the energy expenditure of the activity was established using the metabolic equivalent of task (MET) according to the Compendium of Physical Activity (version 2011; (Ainsworth et al. 2011)). As described in detail in the introduction, section 1.2, the appropriate MET value was assigned to each of the reported activities and the overall amount of PA was calculated as MET-hours per week out of the duration and frequency the patient reported, separately for walking, cycling and sports.

2.3.3.3 Patient-reported outcomes (standardized validated questionnaires)

The following patient-reported outcomes were investigated as possible determinants of exercise attendance and maintenance and assessed with standardized validated questionnaires.

The quality of life was assessed using the 30-item European Organization for Research and Treatment of Cancer quality of life questionnaire for cancer patients (EORTC-QLQ-C30, version 3.0) that encompasses symptom scales (fatigue, pain, nausea and vomiting) and functional scales (physical, role, cognitive, emotional and social functioning) (Aaronson et al. 1993). Further, the financial impact and commonly reported symptoms including dyspnea, insomnia, appetite loss and digestive issues (diarrhea, constipation) are separately assessed (Aaronson et al. 1993). Additionally, other modules of the EORTC questionnaire were used, including the 20-item QLQ-CIPN20 module to investigate the chemotherapy-induced peripheral neurotoxicity (CIPN), EORTC-QLQ-FA13 for fatigue and the 23- item breast cancer specific EORTC module (EORTC-QLQ-BR23) to evaluate any problems with the affected breast or arm, like swelling or pain (Aaronson et al. 1993).

All EORTC modules are scored as described in the third version of the EORTC-QLQ-C30 module (Fayers et al. 2001). All scales have assigned questions (i.e., items) with response options from '1= Not at all' to '4=very much', except the overall health status that has a 7-point Likert scale ranging from '1=very poor' to '7= excellent', that are added together (Fayers et al. 2001). There are no cut-off values yet, but according to the reference values of Karsten and colleagues (2022), a cut-off value of 65 was used for the total EORTC score and according to Friedrich and colleagues (2018) a cut-off of 12 for fatigue to analyze possible differences between patients with high and low scores (Friedrich et al. 2018; Karsten et al. 2022).

Anxiety and depression were assessed with the Patient Health Questionnaire 4 (PHQ-4). This 4-item questionnaire measures the anxiety and depression over the course of the last two weeks on a 4-point Likert scale ranging from the value '0' equaling 'Not at all' to 'Almost every day' with a score of '3' (Lowe et al. 2010). The first two questions assess depression and the last two anxiety. By summing up the respective two scores, a score range of 0 to 6 for either depression and anxiety is obtained (Lowe et al. 2010). A person has depression or anxiety, if the score of the respective value equals 3 or higher, but usually the overall reference value as indicator for psychologic distress is presented by adding the two scales together: 0-2: 'none', 3-5: ‘low’, 6-8: ‘moderate’ and 9-12: ‘high’ levels of psychological distress (Lowe et al. 2010). The fear of falling was assessed using the Falls Efficacy Scale- International (FES-I). The FES-I assesses the patient’s fear of falling while doing certain activities of daily living (Tinetti et al. 1990). Based on a 4-point Likert scale, the patients indicate for each of the 16 activities their fear of falling with 1 = ‘no concern about falling’, 2 = ‘somewhat concerned about falling’, 3 = ‘fairly concerned about falling’, 4 = ‘very concerned about falling’ (Yardley et al. 2005). The scores are added together and may, therefore, range between 16 (‘no concerns at all’) to 64 (‘very concerned’) (Yardley et al. 2005).

To evaluate the perception of social support overall and within family, friends or a significant other person, the patients were asked to complete the Multidimensional Scale of Perceived Social Support (MSPSS), a 12-item questionnaire in which the patients need to indicate on a 7-point Likert scale from ‘very strongly disagree’ to ‘very strongly agree‘ to which extent they agree with the given statements (Zimet et al. 1988). The subscales family, friends and a significant other consist of four questions that are summed up and divided by four to receive the score of the scale, the total score is the sum of the scores of each scale divided by twelve (Zimet et al. 1988). Yet, there are no reference values, but following cut-off values are suggested: 1-2.9: ‘low’, 3-5: ‘moderate’ and 5.1-7: ‘high’ perceived support (Zimet et al. 1988).

All assessed data were pseudonymized collected and digitalized on CRFs that were set up with the TELEFORM® system (Cardiff) after verification in the system and stored in an Microsoft Access database.

2.3.3.4 Medical data

All necessary characteristics were extracted from the patient’s medical record via the medical information system of the university hospital clinic Heidelberg (SAP IS-H), covered by the informed consent form. These characteristics include age, the cancer type, cancer site (left and/or right breast), hormone receptor status, date of diagnosis, scheduled therapy and existing medical history including pre-existing diseases, complaints, and medication. This was repeated at the study assessments directly after completing the chemotherapy and six months after the breast surgery. The patients were asked to complete questionnaires concerning the administration of the neoadjuvant chemotherapy (medication, dosage and schedule performed as planned) and treatments after the surgery. Missing information was added through the medical records and the respective health care practitioner.

All information were continuously updated throughout the study (Table 4).

2.4 Statistical methods

All statistical analyses of the BENEFIT data were conducted with the Statistical Analysis System (SAS, version 9.4), a statistical software from the SAS Institute (Inc., Cary, NC, USA), according to the intent-to-treat principle. The statistical analyses were conducted as complete case analyses.

Every test was performed two-sided with $p < 0.05$ considered statistically significant. Unless differently mentioned, all data are expressed in mean (*M*) and standard deviation (*SD*).

2.4.1 Systematic review and meta-analyses

In the literature-based meta-analysis, standardized mean differences (*SMD*) with 95% confidence intervals (*CI*) were calculated as differences of the mean change from baseline to the respective follow-up measurement between the IG and CG divided by the pooled pre-test SD (Morris 2008). The pooled pre-test SD is calculated according to Morris (2008) as follows (Figure 3) (Morris 2008).

$$SD_{pre} = \sqrt{\frac{(n_T - 1)SD^2_{pre,T} + (n_C - 1)SD^2_{pre,C}}{n_T + n_C - 2}}$$

**C: control group; n: number of patients; pre: pre-test; SD: standard deviation; T: treatment/intervention group*

Figure 3: Formula to calculated the pooled pre-test standard deviation (Morris 2008)

The random effect models were computed with the Cochrane-Software RevMan 5.3. Random effect models were used to consider the heterogeneity between the studies. It is assumed that the effects are normally distributed and follow a certain distribution, but the different effects are considered to be random (Deeks et al. 2022). The effect estimate of an intervention across all included studies is calculated as the weighted mean of the estimated effects of the intervention in each individual study (Deeks et al. 2022). The calculation of the weight is usually performed according to the inverse-variance method, due to which larger studies are given more weight than smaller studies (Deeks et al. 2022). This is done to reduce the uncertainty of the pooled estimation of the pooled effect that is caused by the different magnitudes of the standard error, because larger studies usually have smaller standard errors (Deeks et al. 2022). The weighted average of the intervention is then calculated as the quotient of the sum of estimate and weight divided by the sum of weights (Deeks et al. 2022). The effect sizes with its heterogeneity, mean differences, 95% CI and weights are displayed in forest plots. Thereby, the mean effect is depicted as the core of the distribution with the breadth as its degree of heterogeneity (Deeks et al. 2022). The heterogeneity was here assessed with the Prediction intervals software (www.Meta-Analysis.com/Prediction), because of the small number of studies in each group.

The studies, in which PA variables appeared to have a skewed distribution by having the ratio *mean/SD* < 1.5, were excluded from the meta-analyses but were still included in the systematic review.

2.4.2 Analyses of possible influencing determinants of the attendance at the exercise interventions (BENEFIT study)

To assess the effect of possible influencing factors on the individual attendance at the BENEFIT exercise interventions, a multiple linear regression analysis was conducted. With regard to the literature and theoretical deliberation, the following influencing factors formed the basis of the multiple linear regression model: Randomization to either AT or RT, PA and PE (walking, cycling, sports) in the 12 months prior to the study entry, education, marital status, age, BMI, and the chemotherapy-related side-effects fatigue, nausea and pain. Thereafter the variables regarding having exercised in the youth, having experience with resistance training, being currently employed, having underaged children, anxiety and depression, CIPN, having received the preferred exercise intervention and the travel distance to the training facility (log-transformed) were added one after the other.

To enable meaningful comparisons for the above described objectives, all variables were categorized:

- Age: 1= ‘age ≤ 55 years’, 2= ‘age > 55 years’
- BMI: 1=’BMI ≤ 25’, 2=’BMI > 25’
- Marital status: 0= ‘not married’ (equaling everyone, who is not in a relationship), 1= ‘married/living with a partner’
- Children below the age of 18 years: 0=’No’, 1=’Yes’
- Currently working: 0=’No’, 1=’Yes’
- Educational level: ‘lower education’ (no degree or secondary degree), ‘middle education’ (high school degree) and ‘higher education’ (A-level/diploma qualifying for university or university degree)
- Experience with resistance training: 0=’No’, 1=’Yes’
- Performed physical activity and exercise in the youth: 0=’No’, 1=’Yes’
- Pain: 0= ‘no pain’, 1= ‘mild pain’, 2= ‘moderate pain’, 3= ‘severe pain’
- Nausea: 0= ‘no nausea’, 1= ‘experiencing nausea
- Exercise continuation: 0=’did not continue the exercise intervention’, 1=’continued the exercise intervention’
- Received preferred exercise intervention: 0=’did not receive the preferred exercise intervention’, 1=received the preferred exercise intervention’.
- Rating of the exercise intervention: 1=’very poor’, 2=’poor’, 3=’OK’, 4=’good’, 5=’very good’.

As the performed PA and PE behavior and the travel distance to the training facility appeared to be very skewed, the variables were log-transformed.

Multiple linear regression models to comprehensively investigate the association between possible influencing factors and the attendance at exercise interventions were performed. Differences between the groups for each investigated variable were identified using the Wilcoxon test for not normally distributed variables and the *t*-test for normally distributed variables.

The basic regression model for investigating the influence of several possible influencing factors on exercise attendance included the randomization (AT/RT), age and BMI as continuous variables, marital status (living with a partner: yes/no), educational background (university degree/high school/lower), PA and PE behavior in the 12 months prior to the study entry, including walking, cycling and sports as log-transformed variables and the chemotherapy-related side-effects fatigue, pain, and nausea as being present/not present, to adjust for possible associations between these variables. The other aforementioned variables, i.e., being currently employed, having underaged children, the perceived social support (overall and in its subscales), having received the preferred exercise intervention, the travel distance to the training facility (log-transformed), exercise in the youth (yes/no), and experience with resistance training prior to the study (yes/no) were constituently added to the basic linear regression model to assess an association with exercise attendance. No conflict with the regression assumptions could be observed in neither the fit diagnostic panels nor the variance inflation.

As one patient did not provide information of at least one variable in the basic regression model, she could not be included in the regression model.

2.4.3 Analyses of the maintenance of exercise interventions (BENEFIT study)

Due to the small sample size and a high number of ties, the proportional hazard assumption to carry out Cox proportional hazard analyses was violated. Therefore, the training maintenance of the exercise interventions was investigated with Kaplan-Meier analyses. The duration of the maintenance time was calculated as the time between end of intervention and the time the patients reported to no longer maintain the training, or when they reported to continue the training until the last study assessment (i.e., T5 which took place 24 months post-intervention), they were censored. The differences between the three groups AT, RT and CG were investigated with the log-rank test. The association between possible influencing factors and the training maintenance beyond the exercise intervention was investigated with separate Kaplan-Meier analyses. To compare the categorical variables between the three groups, chi-square (Chi^2) or Fisher's exact tests were used, and Kruskal-Wallis tests for the non-normally distributed metric values. As possible influencing factors, the following variables were hypothesized to be associated with the training maintenance: age, married/living with a partner (yes/no), level of education (low/middle vs. high), employment status at the time of the diagnosis, having children under 18 years of age (yes/no), and the attendance at the exercise interventions. It was hypothesized that younger patients with underaged children may not maintain the training overall or as long as those without children, therefore, a Kaplan-Meier analysis stratified by age (≤ 55 years) and having underaged children (yes/no) was conducted. Alike, older patients may be retired and, therefore, unemployed, thus, a Kaplan-Meier analysis stratified by age (> 55 years) in the unemployed patients was conducted.

To enable meaningful comparisons for the above described objectives, all variables were categorized:

- Age: 1= ‘age ≤ 55 years’, 2= ‘age >55 years’
- BMI: 1=’25 ≤ BMI <30’, 2=’BMI > 25’
- Marital status: ‘married/living with a partner’ or ‘not married’ (equaling everyone, who is not in a relationship)
- Children below the age of 18 years: 0=’No’, 1=’Yes’
- Currently working: 0=’No’, 1=’Yes’
- Educational level: ‘lower education’ (no degree or secondary degree), ‘middle education’ (high school degree) and ‘higher education’ (A-level/diploma qualifying for university or university degree)
- Attendance: 0= ‘0%’, 1= ‘0.1 - <25’, 2= ‘25.1 - <50’, 3= ‘50.1 - <75’, 4= ‘75.1 - <100’

3 Results

The results are associated with three first-authored publications/submitted manuscripts related to this thesis: (Goldschmidt et al. 2024a; Goldschmidt et al. 2024b; Goldschmidt et al. 2022).

3.1 Systematic review and meta-analyses

3.1.1 Results of the systematic search – identified studies

The systematic literature review (described in chapter 2.1) identified 5,036 articles in the four databases Cochrane, Embase, PubMed and Web of Science matching the search criteria (Annex 8.1.1). Of these, 1,759 were duplicates. After reading the title and abstract of the remaining 3,277 articles, 136 were deemed eligible. After reading the full texts of those 136 articles, 27 fulfilled all criteria for the systematic review, covering 4,120 patients with breast cancer (Figure 4).

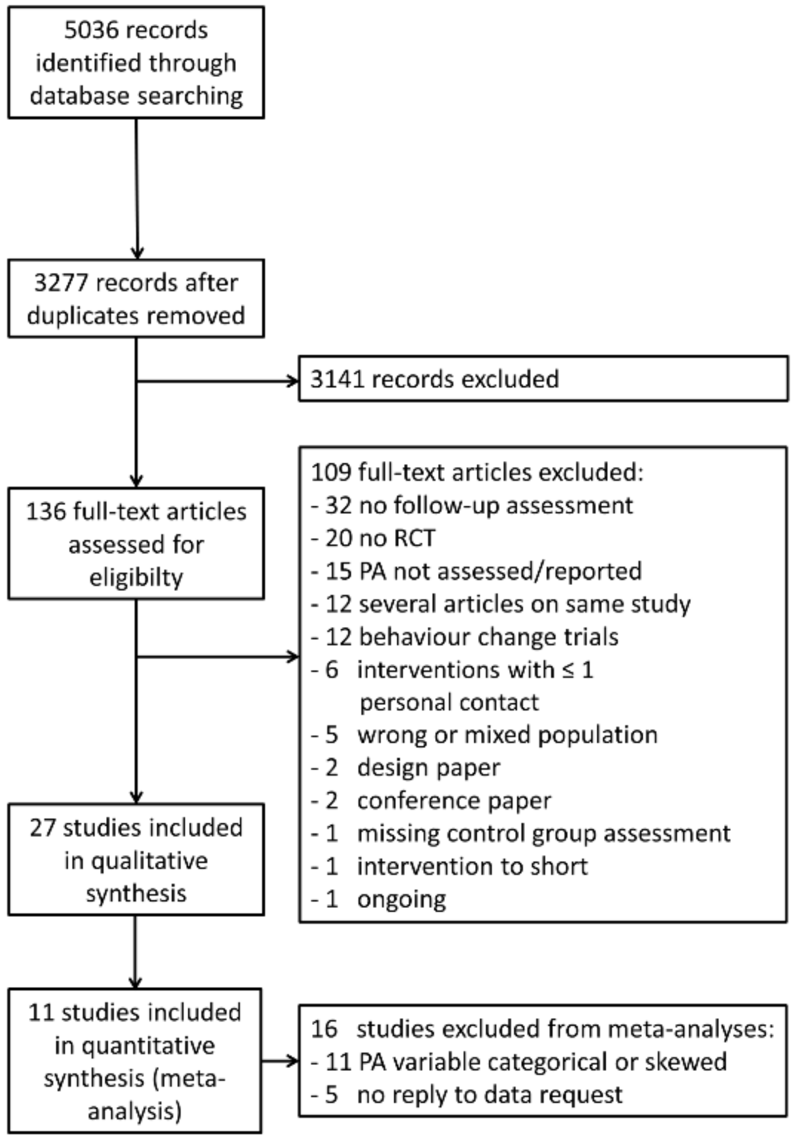


Figure 4: Flowchart of the meta-analyses (Goldschmidt et al. 2022)

The intervention period of the included studies ranged between 4 to 52 weeks and included RT (6 studies), AT (6 studies), compared AT with RT (3 studies) and a combination of AT and RT (12 studies). In almost all studies, training interventions were performed individually. Only one study conducted a group exercise training program (Mutrie et al. 2012). Seven of the interventions were unsupervised, whereas all other interventions were leastwise partly supervised with or without an additional unsupervised training session at home.

After completing the intervention, the studies performed their follow-up assessments between 3- and 60-months post-intervention. The characteristics of the studies included in the systematic review are presented in Table 5.

Table 5: Characteristics of all included studies in the systematic review and meta-analyses (Goldschmidt et al. 2022)

Study	N, age	Intervention period	Intervention	Delivery mode	Duration [weeks]	Frequency, intensity, and further details	Follow-up [months]	Included in meta-analysis
An 2020 (Canada) (An et al. 2020b)	STAN: N= 96 49.2 ± 8.4 HIGH: N=101 50.1 ± 8.8 COMB: N=104 50.5 ± 9.4	adjuvant chemo-therapy	STAN: standard dose of aerobic exercise HIGH: a higher dose of aerobic exercise COMB: combined aerobic and resistance exercise	supervised	12-18	STAN: 75 min/week of vigorous-intensity /3days/week for 25-30 min/ session HIGH: 150 min/week of vigorous-intensity aerobic exercise/3 days/week for 50- 60 min/session COMB: aerobic exercise of STAN group plus a standard resistance exercise program 3 days/week	24	No
Anderson 2012 (USA) (Anderson et al. 2012)	IG CG <50: 21 23 50 to 65: 23 19 65 to <75: 4 7 >75: 4 8	adjuvant chemo-/radio-therapy	IG: tailored exercise, lymphedema prevention, patient and diet education, and counselling CG: information materials	supervised and not supervised home-based	24	IG: twice a week consisting of an aerobic warm up (5 min), 20 min full body workout using hand weights and resistance machines, 10 min stretching twice a week consisting of an aerobic warm up (5 min), 20 min full body workout using hand weights and resistance machines, 10 min stretching	15	no

Table 5 (continued)

Study	N, age	Intervention period	Intervention	Delivery mode	Duration [weeks]	Frequency, intensity, and further details	Follow-up [months]	Included in meta-analysis
Bolam 2019 (Sweden) (Bolam et al. 2019)	RT: 58 53.4 ± 10.1 AT: 54 53.9 ± 9.2 CG: 48 54.1 ± 9.6	adjuvant chemo-therapy	RT: combined resistance and aerobic training AT: aerobic training CG: usual care	supervised	16	60 min/twice weekly RT: 8 machines, 2 sets, 8-12 repetitions at 70%-80% of 1-RM + HIIT on a cycle ergometer: 3x3 min bouts at a rate of perceived exertion (RPE) of 16-18 with one-minute recovery between each bout AT: 20 min moderate intensity (RPE 13-15) and HIIT consisting of 3x3 min bouts at an RPE of 16-18 with one-minute recovery between each bout	20	yes
Carayol 2019 (France) (Carayol et al. 2019)	IG: 72 51.2 ± 10.9 CG: 71 52.1 ± 9.3	adjuvant chemo-therapy	IG: 8-10 MET aerobic and resistance training/week CG: usual care	supervised and not supervised home-based	26	IG: thrice weekly - one session muscle strengthening and two aerobic sessions (HR-related), increasing from 30-40 to 40-50 min per session	18	yes

Table 5 (continued)

Study	N, age	Intervention period	Intervention	Delivery mode	Duration [weeks]	Frequency, intensity, and further details	Follow-up [months]	Included in meta-analysis
Cornette 2015 (France) (Cornette et al. 2016)	*IG: 22 52 (37–73) CG: 22 49 (37–68)	adjuvant or neoadjuvant chemo-therapy	IG: aerobic and resistance training CG: usual care	not supervised home-based	27	IG: 1x/week individually tailored resistance training (2x 8-12 reps) 2x/week aerobic exercise according to HR at VT of CPET	6.75	yes
Daley 2007 (USA) (Daley et al. 2007b)	IG: 34 51.6 ± 8.8 Exercise placebo: 36 50.6 ± 8.7 CG: 38 51.1 ± 8.6	12-36 months after treatment completion	IG: aerobic exercise training Exercise placebo: light-intensity body conditioning (flexibility, stretching) CG: usual care	supervised	8	IG: 3x/week à 50 min moderate aerobic exercise at 65%-85% of age-adjusted HR maximum and RPE of 12 to 13 + PA behavior change	6	no
Foucaut 2019 (France) (Foucaut et al. 2019)	*IG: 41 53.9 (26.2–71.5) CG: 19 49.4 (27.0–69.3)	adjuvant chemo-therapy	IG: outdoor training and indoor fitness + Dietary counselling CG: dietary and PA counselling according the guidelines for cancer survivors	supervised If attendance was not possible, not supervised home-based	24	IG: Twice weekly moderate-to-vigorous (≥ 3 MET) sessions of Nordic walking (60 min) and indoor fitness (45 min) consisting of aerobic-based exercises that involved the major muscles)	12	no

Table 5 (continued)

Study	N, age	Intervention period	Intervention	Delivery mode	Duration [weeks]	Frequency, intensity, and further details	Follow-up [months]	Included in meta-analysis
Hayes 2013 (Australia) (Hayes et al. 2013)	IG: 207 51.7 ± 8.8 CG: 130 53.9 ± 8.3	after surgery	IG: combined aerobic- and resistance based moderate activity CG: usual care	supervised and not supervised	32	IG: supervised: one weekly session with an exercise physiologist not supervised: 180 min + of aerobic- and resistance based moderate activity per week to be accumulated on at least 4 days	12	no
Husebo 2014 (Norway) (Husebø et al. 2014)	IG: 33 50.8 ± 9.7 CG: 34 53.6 ± 8.8	adjuvant chemo-therapy	IG: combined aerobic and resistance training CG: usual care	not supervised home-based	IG: 16.7 ± 7.6 CG: 17.6 ± 7.9	IG: 3x/week resistance training + 30 min brisk walking daily	6	no

Table 5 (continued)

Study	N, age	Intervention period	Intervention	Delivery mode	Duration [weeks]	Frequency, intensity, and further details	Follow-up [months]	Included in meta-analysis
Ibrahim 2018 (Canada) (Ibrahim et al. 2018)	IG: 29 CG: 30 overall: 39.2 ± 5.0	adjuvant radiotherapy	IG: combined strength, endurance, and stretching exercise for the upper body CG: usual care	supervised and not supervised	12	IG: 6-week program of low-level cardiovascular and resistance exercises that progressed to a set of more advanced exercises for the remaining 6 weeks; strength: 8-12 repetitions, endurance: max 20 repetitions; at least once a week supervised and 2-3 times not supervised at home	18	no
Leach 2019 (USA) (Leach et al. 2019b)	One-to-one: 12 51.9 ± 8.3 Group-based: 14 51.8 ± 9.2	completed adjuvant treatment for breast cancer	One-to-one: combined aerobic and resistance training Group-based: combined aerobic and resistance training and PA behavior change information/strategies	supervised	8	One-to-one: 2x/week à 40-55 min: 20-30 min aerobic exercise at 55-75% HRR, 20-25 min muscle strengthening and PA behavior change information/ strategies Group-based: 2x/week à 40-55 min: 20-30 min aerobic exercise at 55-75% HRR, 20-25 min muscle strengthening	3	no

Table 5 (continued)

Study	N, age	Intervention period	Intervention	Delivery mode	Duration [weeks]	Frequency, intensity, and further details	Follow-up [months]	Included in meta-analysis
May 2009 (Netherlands) (May et al. 2009)	PT + CBT: 76 47.8 ± 10.5 PT: 71 49.9 ± 11.3	after completion of cancer treatment	PT + CBT: Combined aerobic and resistance training with group sports and cognitive-behavioral therapy (CBT) PT: Combined aerobic and resistance training with group sports	supervised	12	PT + CBT: 2x 2 sessions/week PT + once weekly CBT for 2 hours: 30 min aerobic and 30 min strength training + 60 min group sports + cognitive-behavioral problem-solving per session PT: 2x 2 sessions/week PT: 30 min aerobic and 30 min strength training + 60 min group sports per session	9	no

Table 5 (continued)

Study	**N, age**	**Intervention period**						
Mazzoni 2021 (Sweden) (Mazzoni et al. 2021)	1. High intensity with BCT: 77 60 ± 12 2. Low intensity with BCT: 81 58 ± 12 3. High intensity without BCT: 71 57 ± 11 4. Low intensity without BCT: 72 60 ± 11	(neo-) adjuvant treatment	Aerobic and resistance training with or without face-to-face self-regulatory behavior change technique (BCT) sessions	supervised and not supervised home-based	24	Supervised: Resistance training - twice weekly - High intensity: alternated 3x6 and 3x10 1-RM - Low intensity: 3x12 repetitions at 50% of 6RM and 3x20 repetitions at 50% of 10RM Not supervised: Aerobic training - twice weekly - High intensity: 20-40 min/session at 80-90% HRR twice per week - Low intensity: 150 min weekly continuous-based exercise at 40-50% HRR	12	no
McNeil 2019 (Canada) (McNeil et al. 2019)	Higher intensity PA: 15 58 ± 10 Lower intensity PA: 15 58 ± 9 CG: 15 60 ± 9	adjuvant chemo-therapy completed	Higher intensity: Aerobic exercise Lower intensity: Aerobic exercise CG: Usual care	supervised	12	Higher intensity: 150 min/week with 60-80% HRR - 15-25 MET/h/week Lower intensity: 300 min/week with 40-59% HRR - 3-5 MET/h/week	6	yes

Table 5 (continued)

Study	N, age	Intervention period	Intervention	Delivery mode	Duration [weeks]	Frequency, intensity, and further details	Follow-up [months]	Included in meta-analysis
Moller 2020 (Denmark) (Møller et al. 2020)	IG: 75 51.5 ± 9.6 CG: 78 52.0 ± 9.3	adjuvant chemo-therapy	IG: health counselling and symptom guidance + group sports CG: health counselling and symptom guidance + step pedometer	supervised	12	IG: 12-week exercise program - six weeks, 9 h/week and six weeks, 6h/week (football games, dance and circuit training) + health counselling and symptom guidance, i.e. 3x/week training + once weekly restorative session	9 months and 3 weeks	no
Mutrie 2012 (Scotland) (Mutrie et al. 2012)	IG: 99 51.3 ± 10.3 CG: 102 51.8 ± 8.7	adjuvant therapy	IG: group exercise programs according to the PA guidelines for cancer patients and survivors CG: usual care	supervised and not supervised home-based	12	IG: 45 min group exercise / twice per week and one home-based training	60	yes

Table 5 (continued)

Study	N, age	Intervention period	Intervention	Delivery mode	Duration [weeks]	Frequency, intensity, and further details	Follow-up [months]	Included in meta-analysis
Penttinen 2019 (Finland) (Penttinen et al. 2019)	IG: 52.8 ± 7.2 CG: 53.3 ± 7.7	recently (within four months) completed adjuvant treatment or started endocrine therapy	IG: supervised and not supervised CG: usual care	supervised and not supervised home-based	52	supervised: 60 min once a week Step aerobics in biweekly rotation with circuit training at an RPE of 14-16 not supervised/home-based: endurance training at least twice a week endurance training CG: encouraged to maintain current PA level	60	no
Pinto 2008 (United States) (Pinto et al. 2008)	IG: 43 53.42 ± 9.08 CG: 43 52.86 ± 10.38	after completion of cancer treatment	IG: telephone intervention CG: contact control	not supervised, home-based	12	IG: promote PA to engage in moderate aerobic exercise at 55-65% HR max from 10 min on two days weekly to 30 min on five days weekly	9	no

Table 5 (continued)

Study	N, age	Intervention period	Intervention	Delivery mode	Duration [weeks]	Frequency, intensity, and further details	Follow-up [months]	Included in meta-analysis
Rogers 2009 (United States) (Rogers et al. 2009)	IG: 21 52 ± 15 CG: 20 54 ± 8	At least 8 weeks post-surgery, taking aromatase inhibitor or estrogen receptor modulator	IG: aim - 150 min MVPA/week CG: written materials	not supervised	12	IG: first 6 weeks: 12 individual exercise sessions with an exercise specialist + first 8 weeks: 6 discussion group sessions with a clinical psychologist + final 6 weeks: 3 individual counseling sessions with an exercise specialist in order to start and maintain 150 min MVPA/week written materials about physical activity were available through the American Cancer Society	6	yes

Table 5 (continued)

Study	N, age	Intervention period	Intervention	Delivery mode	Duration [weeks]	Frequency, intensity, and further details	Follow-up [months]	Included in meta-analysis
Rogers 2015 (United States) (Rogers et al. 2015)	IG: 110 54.9 ± 9.3 CG: 112 53.9 ± 7.7	At least 8 weeks post-surgery, not scheduled for chemo- or radiotherapy	IG: aim: 150 min MVPA/week CG: written materials	not supervised	12	IG: first 6 weeks: 12 individual exercise sessions with an exercise specialist + first 8 weeks: 6 discussion group sessions with a clinical psychologist + final 6 weeks: 3 individual counseling sessions with an exercise specialist in order to start and maintain 150 min MVPA/week CG: written materials about physical activity were available through the American Cancer Society	6	yes
Schmidt 2017 (Germany) (Schmidt et al. 2017)	IG: 49 52.2 ± 9.9 CG: 46 53.3 ± 10.2	adjuvant chemo-therapy	IG: machine-based resistance training CG: Progressive muscle-relaxation	supervised	12	IG: 60 min/twice weekly; per session: 8 machines, 3 sets, 8-12 repetitions at 60%-80% of 1-RM CG:60 min/twice weekly: progressive muscle relaxation according to Jacobsen	12	yes

Table 5 (continued)

Study	N, age	Intervention period	Intervention	Delivery mode	Duration [weeks]	Frequency, intensity, and further details	Follow-up [months]	Included in meta-analysis
Steindorf 2014 (Germany) (Steindorf et al. 2014)	IG: 80 55.2 ± 9.5 CG: 80 56.4 ± 8.7	adjuvant radiotherapy	IG: machine-based resistance training CG: progressive muscle-relaxation	supervised	12	IG: 60 min/twice weekly; per session: 8 machines, 3 sets, 8-12 repetitions at 60%-80% of 1-RM CG: 60 min/twice weekly: progressive muscle relaxation according to Jacobsen	12	yes
Thorsen 2005 (Norway) (Thorsen et al. 2007)	IG: 69 (21 BRCA) 39.0± 8.4 CG: 70 (21 BRCA) 39.1 ± 8.6	after completion of primary cancer treatment	IG: Aerobic exercise CG: usual care	supervised home-based	14	IG: Minimally twice a week à 30 min, intensity was chosen according the BORG scale 13-15 (equivalent to slightly strenuous to strenuous) without a heart rate monitor and 60%-70% of maximal heart rate	12	no

Table 5 (continued)

Study	N, age	Intervention period	Intervention	Delivery mode	Duration [weeks]	Frequency, intensity, and further details	Follow-up [months]	Included in meta-analysis
vanWaart 2015 (Netherlands) (van Waart et al. 2015)	Onco-Move: 77 50.5 ± 10.1 OnTrack:76 49.9 ± 8.4 CG: 77 51.6 ± 8.8	Adjuvant chemo-therapy	Onco-Move: aerobic exercise OnTrack: moderate-to-high combined resistance and aerobic exercise CG: usual care	Onco-Move: not supervised home-based OnTrack: supervised		OncoMove: low-intensity, individualized, self-managed PA, special trained nurses encouraged participants to engage in at least 30 min of PA/day for 5 days (BORG 12-14) OnTrack: around 50 min twice per week supervised: 20 min resistance training with 2x8 series at 80% 1-RM and 30 min aerobic exercise at 50%-80% max workload and engaged to be active 30 min/5 days not supervised	6	yes

Table 5 (continued)

Study	N, age	Intervention period	Intervention	Delivery mode	Duration [weeks]	Frequency, intensity, and further details	Follow-up [months]	Included in meta-analysis
Witlox 2018 (Netherlands) (Witlox et al. 2018)	IG: 102 49.7 ± 8.2 CG: 102 49.5 ± 7.9	Six weeks after diagnosis irrespective of therapy	IG: combined resistance and aerobic exercise CG: usual care	supervised and not supervised	18	IG: supervised: 1h/twice a week combined resistance training for major muscle groups based on 1-RM and aerobic interval training based on CPET- HR at VT Not supervised: being moderate active for 30 min a day - at least thrice weekly	48	yes

**median age (range)*

AR - activity restrictions, AT – aerobic training, BCT - behavior change techniques, BRCA – Breast cancer, CBT - cognitive-behavioral therapy, CG – control group, COMB – high dose of combined aerobic and resistance exercise, CPET-Cardiopulmonary Exercise Testing, HI – high intensity, HIGH – high dose of aerobic exercise, HR-Heart rate, HRR - heart rate reserve, IG – intervention group, LI – low intensity, MET- metabolic equivalent of task, MVPA-moderate-to-vigorous-PA, NAR – no activity restrictions, PASE - Physical Activity Scale for the elderly, PT -physical training, 1-RM – one-repetition maximum, RT- resistance training, STAN- Standard dose of aerobic exercise, SQUASH- Short Questionnaire to Assess Health-enhancing physical activity, RPE - rating of perceived exertion, VT- ventilatory threshold

The rated methodological quality according to the Cochrane risk of bias tool for each study is summarized in Annex 8.1.3, Figure 25 and described by study in Annex 8.1.3, Figure 26.

Exercise intervention studies do not enable the blinding of participants due to the nature of the studies, thus, all included RCTs were classified as having high performance bias. The assessment of the PA variables through accelerometry, i.e., objective assessment, was rated as low risk of detection bias, whereas subjectively, i.e., self-reported PA assessed through questionnaires, is unblinded and may be at risk for over- or socially desired reporting, thus at high risk for detection bias.

If a study was rated at high risk of bias in ≥3 categories, it was excluded in the sensitivity analyses to evaluate the impact of the respective studies on the observed effect.

3.1.2 Results of the systematic review

The results of the studies that could not be included in the meta-analysis due to missing data (Anderson et al. 2012; Mustian et al. 2009; Thorsen et al. 2007), skewed PA variables (Husebø et al. 2014; Ibrahim et al. 2018; Pinto et al. 2008) or PA results reported as categorical variables (Daley et al. 2007b; Foucaut et al. 2019; Hayes et al. 2013; Møller et al. 2020) and some additional important results of studies that were included in the meta-analysis are summarized in Table 6.

Table 6: Qualitative summary of important results of the 11 studies that were not included in the meta-analysis and 6 studies included in the meta-analysis, but including additional important results (Goldschmidt et al. 2022)

Study	Sign. effect	Follow-up in months post-intervention	Results considering physical activity (PA) outcomes not included in the meta-analysis
Anderson 2012 (Anderson et al. 2012)	(yes)	15	Participation in PA measured in pedometer steps was observed to be positively correlated with the distance covered in the 6-min walk test at the baseline assessment (p<0.05). At 18 months, the IG covered significantly more meters in the 6-min walk test than the CG: Adjusted mean (SE): 593.2 (13.0) vs. 558.9 (11.8), p=0.0098
Daley 2007 (Daley et al. 2007b)	yes	4	The proportion of participants who were inactive at baseline and increased their PA to become active at least 3 times per week at the end of the 8-week intervention period and 16 weeks later were significantly (p < .001) higher in the IG than in the usual care CG: 82% vs. 9% and 58% vs. 8%, respectively.
Foucaut 2019 (Foucaut et al. 2019)	no	12	Median duration (h/week) of MVPA (≥3 MET) and of VPA (≥4 MET) improved in both groups from BL to 12 months post-intervention with no significant group x time interaction (p=0.40 and 0.11, respectively). MVPA median (min, max), h/week: IG: BL: 14.3 (2.7, 28.2), 12 months: 14.8 (3.1, 29.9) CG: BL: 14.3 (4.7, 27.3), 12 months: 16.2 (7.1, 55.5) VPA median (min, max), h/week: IG: BL: 0.4 (0.0, 8.3), 12 months: 1.7 (0.0, 10.8) CG: BL: 0.6 (0.0, 7.0), 12 months: 1.3 (0.2, 5.8)
Hayes 2013 (Hayes et al. 2013)	no	2	Median (Q1, Q3) MVPA minutes: Face to Face: BL: 120 (5, 257.5) 2 months: 180 (0,840) Telephone: BL: 7.5 (0, 127.5) 2 months: 120 (0,1110) Usual care: BL: 45 (0, 125) 2 months: 120 (0,1120)
Husebo 2014 (Husebø et al. 2014)	no	6	MET-minutes/week from IPAQ, mean (SD): IG: BL: 1333.66 (1367.67), 3 months: 2105.63 (2104.75) CG: BL: 1138.00 (1148.81), 3 months: 1844.94 (1555.35) There were no significant differences in changes in mean levels IG and CG. The walking distance 6 months after chemotherapy completion was significantly improved in both groups. >>>> Data not included in the meta-analysis, because it seemed skewed (in part mean/SD < 1.5)
Ibrahim 2018 (Ibrahim et al. 2018)	?	15	The CG performed more PA than the IG 3 months after the intervention. Both groups returned to pre-diagnosis PA levels about 15 months after intervention. >>>> Data not included in the meta-analysis, because it seemed skewed (in part mean/SD < 1.5)

Table 6 (continued)

Study	Sign. effect	Follow-up in months post-inter-vention	Results considering physical activity (PA) outcomes not included in the meta-analysis
Moller 2020 (Møller et al. 2020)	yes	9.3	Both groups (supervised exercise, pedometer intervention) significantly increased moderate PA during the intervention and maintained it until 9 months after the intervention. Thereby, the supervised exercise group had significantly higher PA values than the pedometer group.
Mustian 2009 (Mustian et al. 2009)	yes	3	Mixed population including 27 breast and 11 prostate cancer patients ANCOVA showed significantly more daily steps walked, minutes of resistance exercise, and resistance exercise days post-intervention and at the 3-month FU in IG than CG (all p values < 0.05). Daily steps, IG vs. CG: BL: 7,222.2 ± 2,691.3 vs. 5,544.9 ± 2,746.7 3 months FU: 12,878 ± 7,570.1 vs. 5,180.8 ± 3,258.9 Daily resistance exercise [minutes], IG vs. CG BL: 1.16 ± 2.95 vs. 1.57 ± 4.73 3 months FU: 8.00 ± 10.26 vs. 0.73 ± 3.03 Days/week of resistance exercise, IG vs. CG BL: 0.21 ± 0.54 vs. 0.21 ± 0.63 3 months FU: 1.56 ± 2.50 vs. 0.12 ± 0.49
Mutrie 2012 (Mutrie et al. 2012)***	no	6, 18, 60	The significant increase in self-reported minutes of the intervention group regarding moderate PA per week during the intervention was not maintained until the 6-month follow-up. 60 months after the intervention, the IG reported around 200 minutes PA per week more than the CG.
Penttinen 2019** (Penttinen et al. 2019)	no	48	No significant differences between IG and CG in change of PA from baseline to the 4-year follow-up. In contrary, CG patients were actually more physically active than IG patients after the end of the 1-year intervention.
Pinto 2008 (Pinto et al. 2008)	yes	3, 6	Significant between-group differences in MVPA at the end of a 12-week intervention vanished 3 months post-intervention, but were significant again 6 months post-intervention. >>>> Data not included in the meta-analysis, because it seemed skewed (in part mean/SD < 1.5)
Rogers 2015 (Rogers et al. 2015)***	yes	3	At the 3-month follow-up, participants of the IG were significantly more likely to meet PA recommendations than CG (Accelerometry assessed PA: OR=2.4 (95%CI: 1.1 - 5.3), self-reported PA: OR=4.8 (95%CI: 2.3 - 10.0)) Proportions meeting PA recommendations: Accelerometry IG: BL: 49.8%, 3 months: 67.4% CG: BL: 49.8%, 3 months: 53.6% Self-report IG: BL: 8.7%, 3 months: 45.6% CG: BL: 2.8%, 3 months: 17.7%
Sagen 2009 (Sagen et al. 2009)	no	24	No group differences regarding PA at the 2-year follow-up measurement.

Table 6 (continued)

Study	Sign. effect	**Follow-up in months post-inter-vention**	**Results considering physical activity (PA) outcomes not included in the meta-analysis**
Schmidt 2015 (Schmidt et al. 2015)*** & Steindorf 2014 (Steindorf et al. 2014) *, ***	no	12	Proportions of patients self-reporting any exercise at 12 months post-intervention were similar to pre-diagnosis levels in IG and CG: IG: pre-diagnosis: 67.5%, 12 months: 68.0% CG: pre-diagnosis: 67.0%, 12 months: 72.0% However, the resistance training intervention appeared to influence the type of exercise performed, with strength exercise being the most common type of exercise at follow-up in the resistance exercise IG, conducted more frequently than in the CG.
Thorsen 2007 (Thorsen et al. 2007)	no	12	At the 6- and 12-month follow-ups, no intergroup differences in types of performed activities or the numbers of activities per patients were observed.
Van Waart 2015 (van Waart et al. 2015)***	no	6	No significant group differences observed between OnTrack, OncoMove and UC neither post-intervention nor at the 6-month FU regarding PA.
Witlox 2018 (Witlox et al. 2018)***	yes	4.5, 43.5	The number of participants meeting the aerobic exercise guidelines was similar in IG and CG 4.5 months post-intervention, but 43.5 months post-intervention more patients achieved aerobic exercise guidelines in IG than CG: BL: 54.4% vs. 51.7% 4.5 months FU: 30.0% vs. 33.0% 43.5 months FU: 72.1% vs. 64.3% 43.5 months post-intervention: IG reported significantly more MVPA than CG (between-group difference 141.46 min/week, 95%CI: (1.31, 281.61), effect size = 0.22) [Population including besides breast cancer also few colon cancer patients]

BL- Baseline, IG - Intervention group, CG - control group, FU- Follow-up, MET – metabolic equivalent of task, MVPA – moderate-to-vigorous physical activity, SD- standard deviation, PA- physical activity, Q1 – first quartile, SE – standard error, VPA – vigorous PA
** published in Schmidt et al. 2017 (Schmidt 2017)*
*** also published in Vehmanen 2021 (Vehmanen et al. 2021)*
**** included in the meta-analyses*

The systematic qualitative review revealed that the exercise interventions had either no or a positive effect on the medium- to long-term PA behavior, represented as no change or improvements of the PA behavior prior to the exercise intervention up to the respective post-intervention follow-up assessment several months after completing the exercise intervention.

The comparison between IG and CG revealed mixed results regarding any differences between IG and CG. Significant group differences in favor of the IG were reported by some studies (Ibrahim et al. 2018; Sagen et al. 2009; Schmidt 2017; Steindorf et al. 2014; Thorsen et al. 2007), but these were not maintained for a longer time after completing the exercise intervention. Yet, some of these studies observed the return to the PA behavior prior to diagnosis (Ibrahim et al. 2018; Schmidt 2017; Steindorf et al. 2014; Thorsen et al. 2007). Some studies reported that the CG improved their PA behavior comparably to the IG (Foucaut et al. 2019; Hayes et al. 2013; Husebø et al. 2014; Møller et al. 2020; Penttinen et al. 2019; van Waart et al. 2015). The remaining studies observed a continuously higher PA behavior of the IG compared to the CG that either persisted over time (Anderson et al. 2012; Daley et al. 2007b; Mustian et al. 2009; Rogers et al. 2015) or disappeared at the first follow-up post-intervention, but was present again some months (Pinto et al. 2008) or years (Mutrie et al. 2012; Witlox et al. 2018) thereafter.

All studies that compared exercise interventions with each other are summarized in Table 7.

Table 7: Qualitative summary of results of studies comparing different exercise interventions (Goldschmidt et al. 2022)

Study	Follow-up in months post-intervention	Results considering PA outcomes after different interventions
An 2020 (An et al. 2020b)	6, 12, 24	Meeting resistance exercise guidelines: COMB significantly superior to HIGH at 6 and 24 months. STAN vs. HIGH vs. COMB BL: 21.9% vs. 18.8% vs. 23.1% 6 months: 42.4% vs. 32.6% vs. 52.0% 12 months: 39.6% vs. 36.8% vs. 45.9% 24 months: 39.3% vs. 28.4% vs. 42.3% Meeting aerobic exercise guidelines: HIGH significantly superior to COMB at 6 months. No significant difference between STAN and HIGH. STAN vs. HIGH vs. COMB BL: 31.3% vs. 28.7% vs. 30.8% 6 months: 62.0% vs. 64.2% vs. 49.5% 12 months: 67.0% vs. 63.2% vs. 67.3% 24 months: 60.7% vs. 56.8% vs. 54.6%
Hayes 2013 (Hayes et al. 2013)	2	Median (Q1, Q3) total PA minutes: Face to Face vs. Telephone vs. Usual care BL 120 (5, 257.5) vs. 7.5 (0, 127.5) vs. 45 (0, 125) 2 months 180 (0,840) vs. 120 (0,1110) vs. 120 (0,1120)
May 2009 (May et al. 2009)	6, 9	No significant group differences in PA were observed between PT and PT+CBT. Compared to baseline, PA was significantly improved in PT and PT+CBT post- intervention and in the 6-month follow-up, and the post-intervention PA values for both groups were maintained until 9-month post-intervention. Thus, adding CBT to a supervised group-based self-management PT did not further enhance the beneficial effects of physical training alone.

Table 7 (continued)

Study	Follow-up in months post- inter-vention	Results considering PA outcomes after different interventions				
Mazzoni 2021 (Sweden) (Mazzoni et al. 2021)	12	Participants, N (%), maintaining PA levels at 12 months follow-up in relation to post-intervention:				
			With BCT		without BCT	
			HI	LMI	HI	LMI
		Aerobic only	61 (79)	54 (67)	40 (56)	51 (71)
		Moderate	35 (45)	30 (37)	28 (39)	27 (38)
		Vigorous	47 (61)	46 (57)	26 (37)	42 (58)
		Moderate-to-vigorous	35 (45)	29 (36)	26 (37)	27 (38)
		Resistance only	2 (3)	1 (1)	2 (3)	0 (0)
		Aerobic and resistance	3 (4)	4 (5)	4 (6)	1 (1)
		More participants with self-regulatory behavior change techniques (BCTs) maintained their PA than those without BCT (1.8 times the odds)				
vanWaart 2015 (van Waart et al. 2015)	6	No significant group differences between OnTrack, OncoMove and CG neither post-intervention nor at the six-month FU regarding PA were observed.				

BCT - behavior change techniques, BL- Baseline, CBT - cognitive-behavioral therapy, CG - control group, COMB – high dose of combined aerobic and resistance exercise, HI – high intensity, HIGH – high dose of aerobic exercise, IG - Intervention group, FU- Follow-up, LMI – low-to-moderate intensity, MET- metabolic equivalent of task, MVPA – moderate-to-vigorous physical activity, N – number, SD-standard deviation, PA- physical activity, PT -physical training, Q1 – first quartile , SD – standard deviation, STAN- Standard dose of aerobic exercise

The comparison of an exercise intervention with and without an additional cognitive-behavioral intervention revealed no significant group differences, thus the PA behavior did not improve (May et al. 2009). But in contrast, another study observed improvements in the PA behavior with a self-regulatory behavior change technique additional to an exercise intervention compared to a solely exercise intervention (Mazzoni et al. 2021). Comparisons of two aerobic exercise interventions of two different intensities revealed no significant group differences, but outperformed the group that received a combined aerobic and resistance exercise intervention in meeting the aerobic exercise guidelines, which outperformed the other two groups in meeting the resistance guidelines (An et al. 2020b).

The comparisons of the intervention delivery method, i.e., supervised versus unsupervised, revealed either no group differences (van Waart et al. 2015) or a slight superiority of individually supervised interventions compared to overall supervised or unsupervised interventions (Hayes et al. 2013).

3.1.3 Results of the meta-analyses

Of the 27 studies included in the systematic review, the PA variables of 11 studies were too skewed and were thus excluded from the meta-analysis. Additionally, 5 studies had missing data that were not provided, even after multiple attempts to get in touch. Thus, overall 11 studies comprising 1,545 patients (IG: 850, CG: 695) could be included in the quantitative meta-analyses.

The reported PA variables were assessed as a self-report through questionnaires in seven studies and objectively through accelerometry in four studies (Bolam et al. 2019; McNeil et al. 2019; Rogers et al. 2015; Rogers et al. 2009) (Annex 8.1.2, Table 19).

The PA variables were either classified as 'total PA' or 'moderate-to-vigorous PA' relative to the included activities and the follow-up study assessments were grouped by the time in months at which the follow-up assessment was conducted (i.e., approximately 3 months, because one study assessed the follow-up assessment 2 and one 4 months post-intervention, about 6 months, because one study had an measurement point 6.2 months post-intervention, 12-20 months, and 43.5-60 months, which contained of only 2 studies).

The investigation of an effect of exercise interventions on the total PA behavior revealed a tendency to a sustainable effect up to 60 months after completing an exercise intervention (SMD [95% CI] = 0.29 [-0.31, 0.90]; p = 0.34) (Figure 5). This effect was statistically not significant (p-values between 0.06 to 0.34) and had only small effect sizes with SMDs between 0.12 to 0.29. Sensitivity analyses did not change the observation (Annex 8.1.4, Figure 27). A sensitivity analysis could not be conducted for the longest follow-up assessment point of 43.5 to 60 months post-intervention as this time point consisted of two studies only, which were both at high risk of bias.

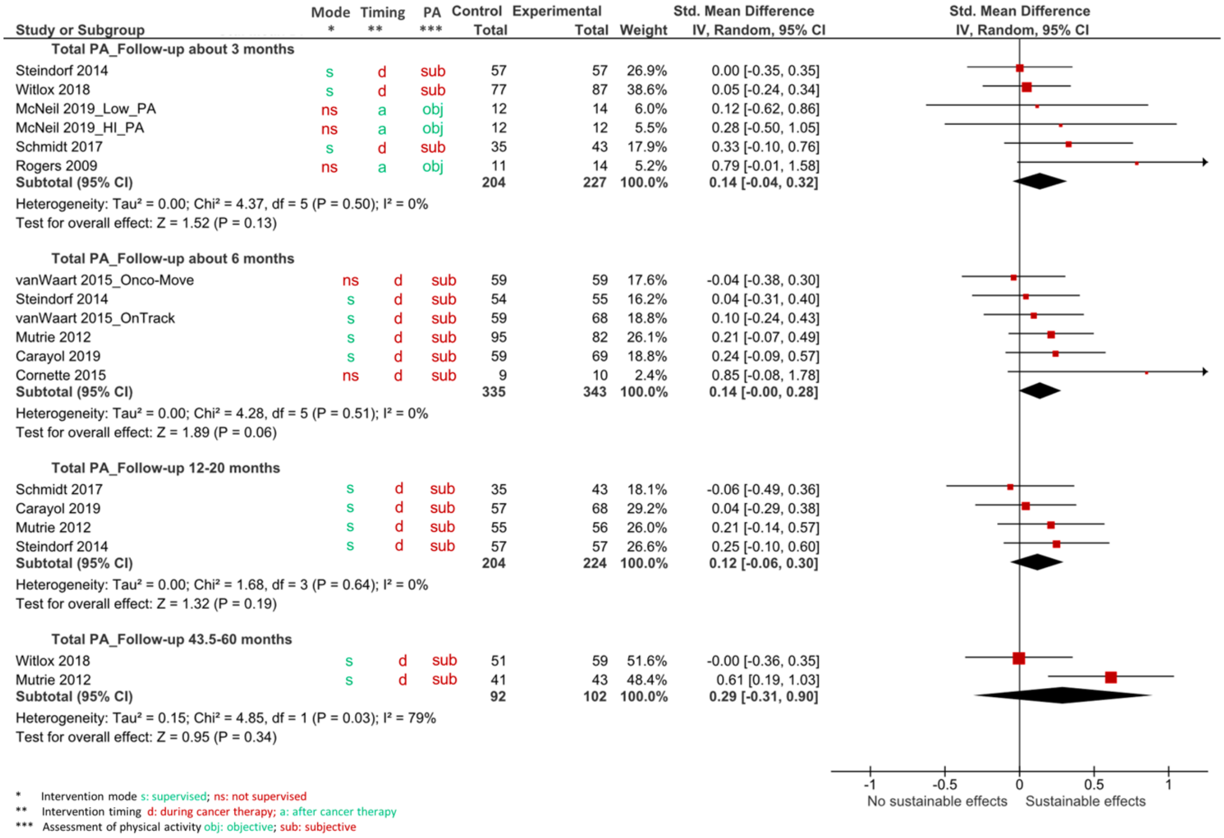


Figure 5: Forest plot for the sustainability of exercise interventions on the outcome total physical activity (Goldschmidt et al. 2022)

The investigation of an effect of exercise interventions on MVPA behavior revealed a tendency to a sustainable effect up to 20 months post-intervention (SMD [95% CI] = 0.14 [-0.06, 0.35]; p = 0.18) that decreased over time (Figure 6). At the 3 months post-intervention follow-up assessment, the effect had a small-to-moderate effect size that failed statistical significance (SMD [95% CI] = 0.41 [-0.03, 0.85]; p = 0.07), but reached significance 6 months post-intervention (SMD [95% CI] = 0.39 [0.07, 0.70]; p = 0.02) and thereafter decreased to a small, statistically not significant effect 12-20 months post-intervention (SMD [95% CI] = 0.14 [-0.06, 0.35]; p = 0.18). Sensitivity analyses did not change the observation (Annex 8.1.5, Figure 28).

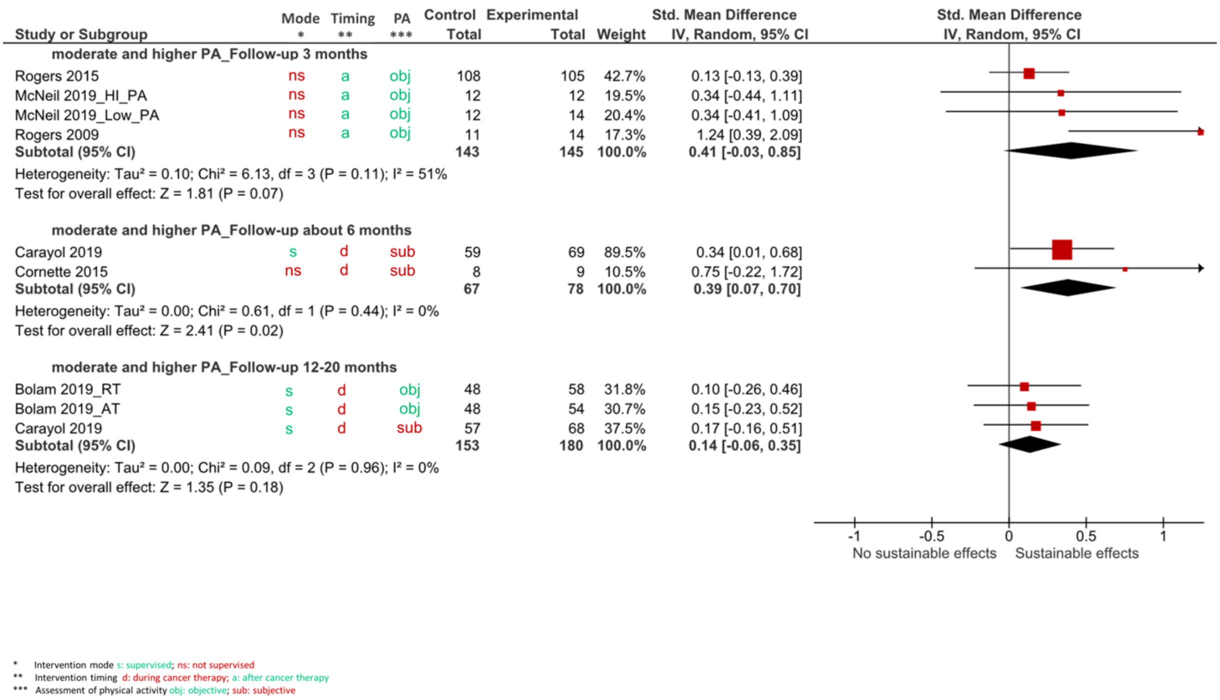


Figure 6: Forest plot for the sustainability of exercise interventions on the outcome moderate-to-vigorous physical activity (Goldschmidt et al. 2022)

The investigation of subjectively and objectively assessed PA revealed inconclusive results due to the number of studies that assessed PA objectively, which additionally had only one follow-up assessment.

For the outcome total PA behavior, PA was assessed objectively in 3 studies with a follow-up assessment of 3 months post-intervention only. The comparison of a subjective versus objective PA-assessment on the total PA behavior revealed a slightly higher, though statistically not significant effect for objective PA-assessment (SMD [95% CI] =0.38 [-0.07, 0.82]; p = 0.10) than for subjectively assessed PA (SMD [95% CI] =0.09 [-0.10, 0.29]; p = 0.36) (Figure 7).

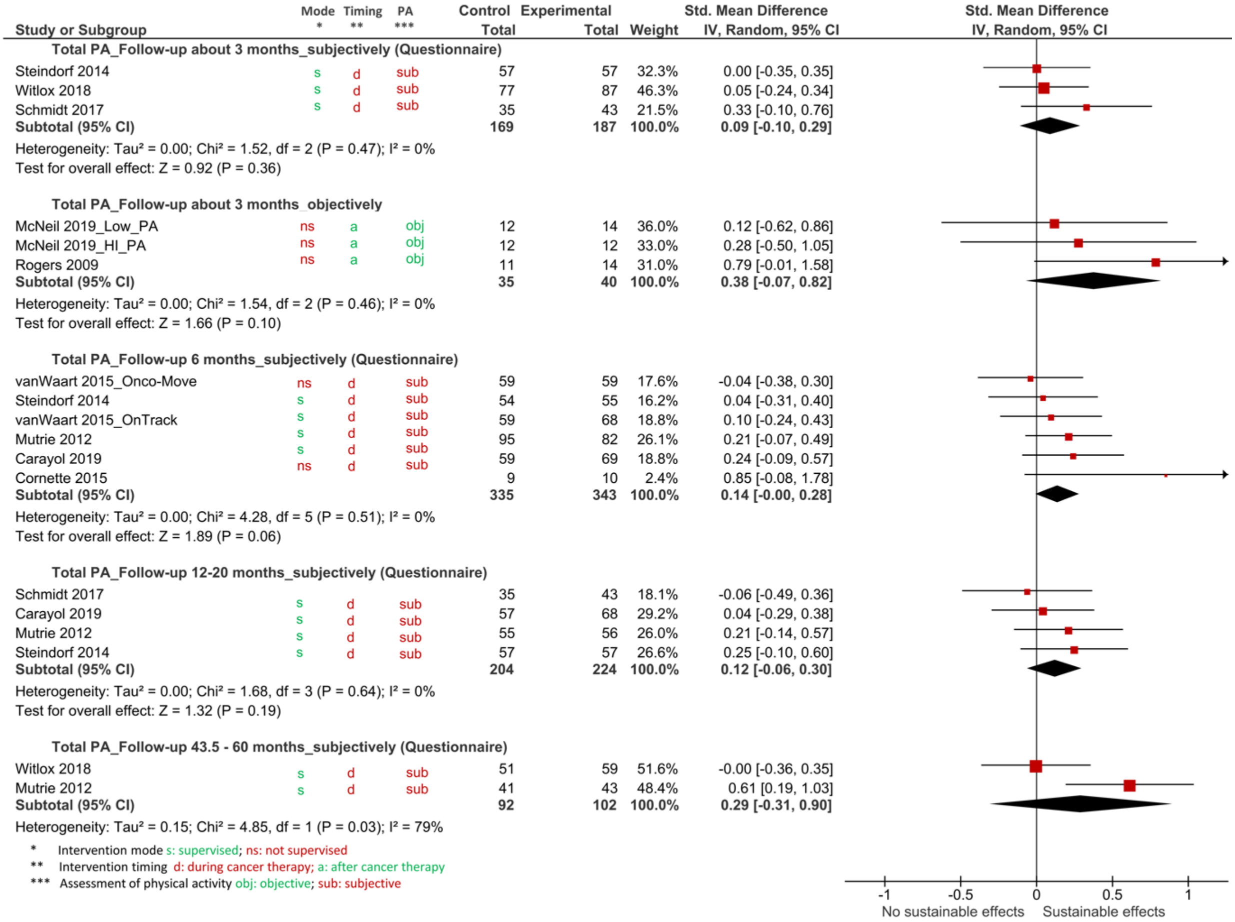


Figure 7: Forest plots for total physical activity, stratified by type of physical activity assessment (objective versus subjective) (Goldschmidt et al. 2022)

For the outcome MVPA behavior, no comparisons could be conducted, because the studies had the same PA-assessment mode within their stratification and time interval (Figure 8). Considering the overall effect, a moderate effect for objective PA-assessment could be observed around 3 months (*SMD* [95% CI] =0.40 [-0.03, 0.85]; *p* = 0.07) as well as 20 months (*SMD* [95% CI] =0.12 [-0.14, 0.38]; *p* = 0.36) post-intervention. Alike, moderate effects were observed for subjectively assessed PA at around 6 months (*SMD* [95% CI] =0.17 [-0.16, 0.51]; *p* = 0.02) and 12 months post-intervention (*SMD* [95% CI] =0.17 [-0.16, 0.51]; *p* = 0.31). The results are based on two studies assessing PA subjectively (one study 6 and one 6- and 12-months post-intervention) and four studies that assessed PA objectively (three studies 3 months, and one study 20 months post-intervention).

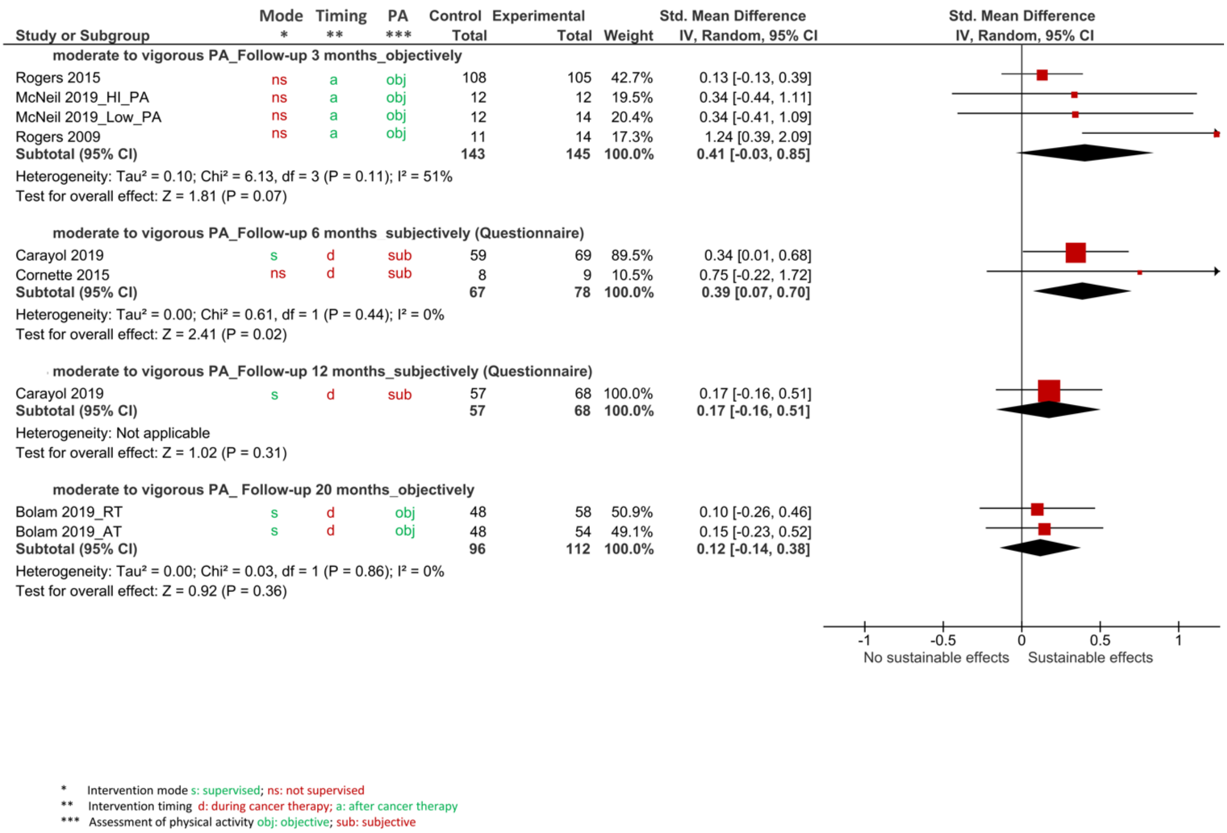


Figure 8: Forest plots for moderate-to-vigorous physical activity, stratified by type of physical activity assessment (objective versus subjective) (Goldschmidt et al. 2022)

The investigation of supervised and unsupervised exercise interventions revealed inconclusive results due to the large confidence intervals and the small number of studies.

For the outcome total PA behavior, the follow-up assessments 3- and 6-months post-intervention could be compared only, because the longer follow-up assessments of 12-20 and 43.5-60 months had no unsupervised intervention to be compared with (Figure 9). The comparison of a supervised versus unsupervised exercise intervention revealed slightly higher effects for unsupervised interventions 3 months (SMD [95% CI] =0.38 [-0.07, 0.82]; p = 0.10) and 6 months post-intervention (SMD [95% CI] =0.30 [-0.55, 1.15]; p = 0.49).

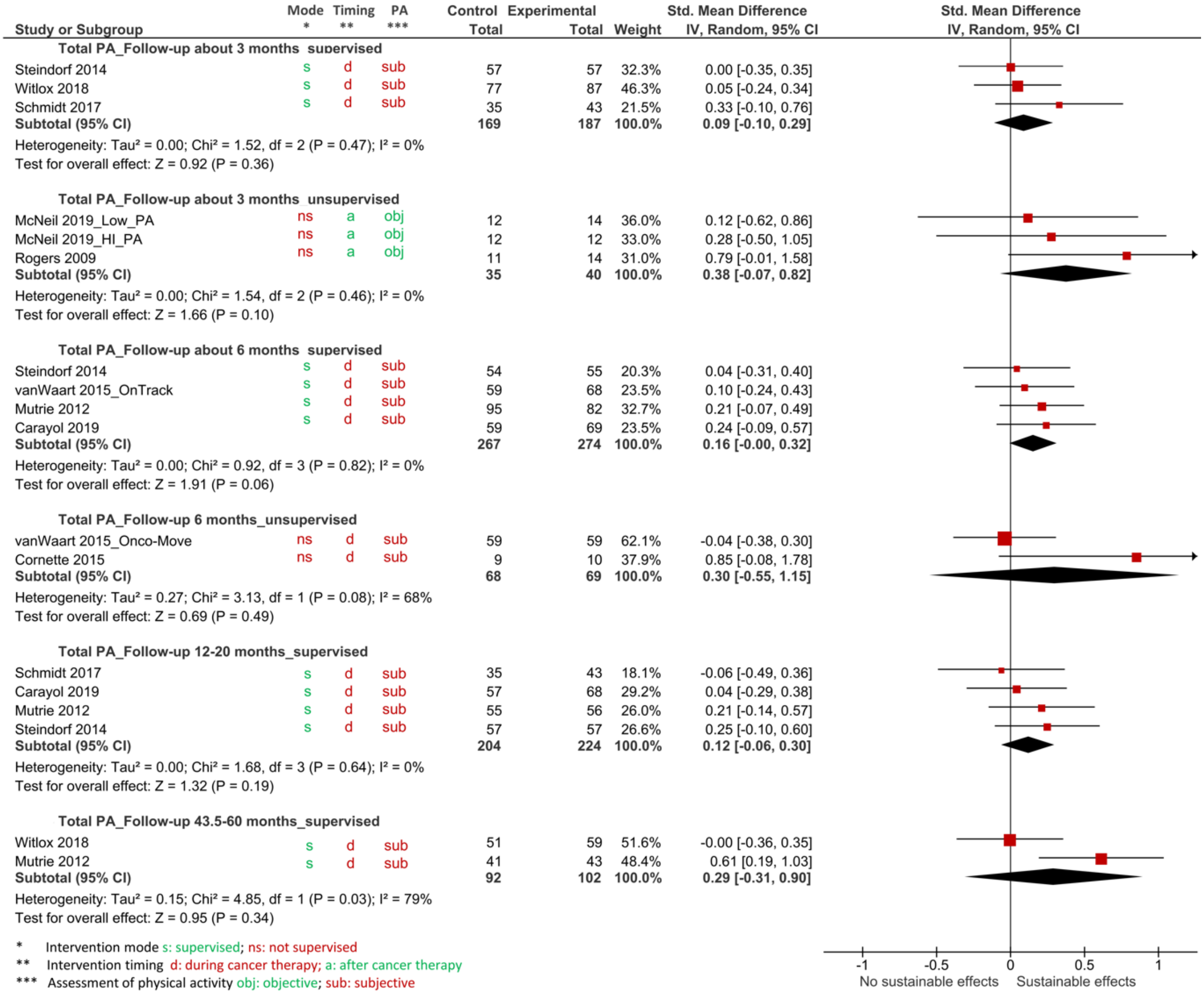


Figure 9: Forest plots for total physical activity, stratified by intervention delivery mode (supervised versus unsupervised) (Goldschmidt et al. 2022)

For the outcome MVPA behavior, no comparisons could be conducted, because the only comparable time interval that was represented in both delivery modes, contained only one study each (Figure 10). The overall effect was not considered, because every time interval, except that 3 months post-intervention consisted of only one study.

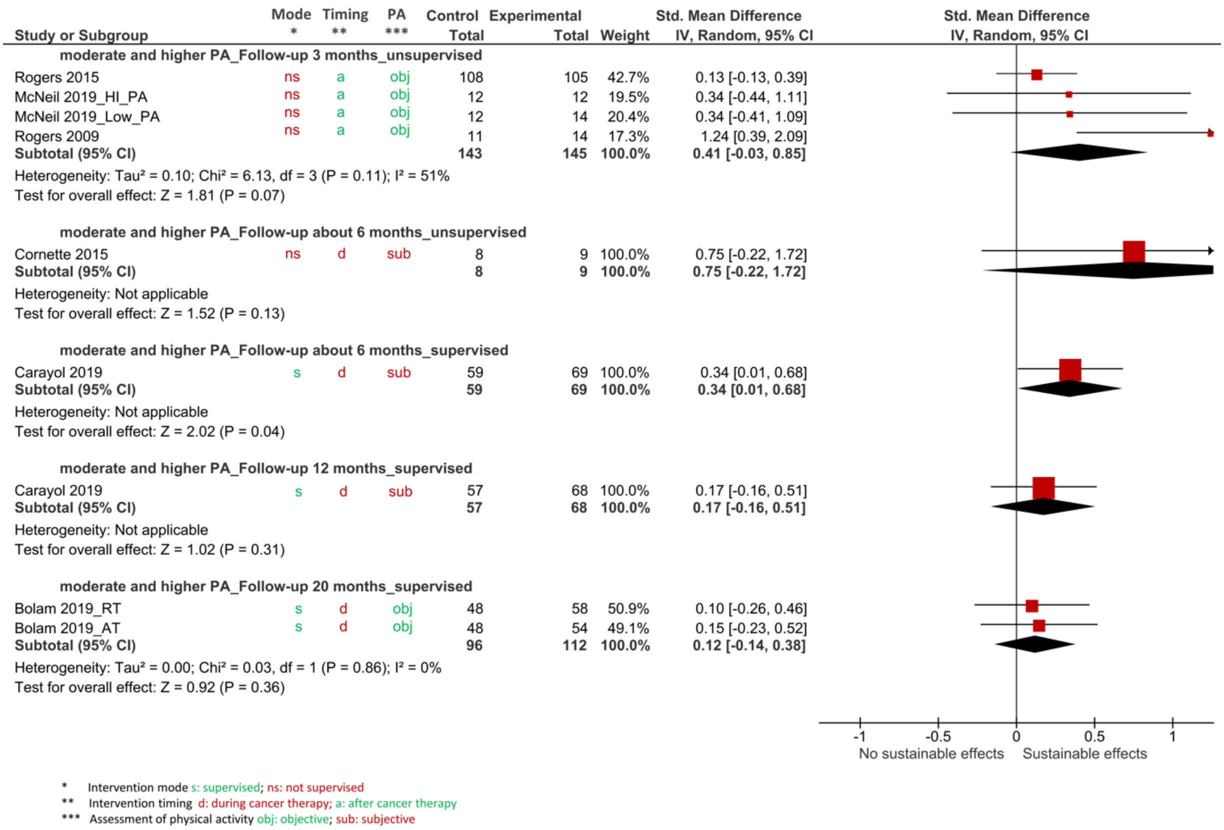


Figure 10: Forest plots for moderate-to-vigorous physical activity, stratified by intervention delivery mode (supervised versus unsupervised) (Goldschmidt et al. 2022)

Further analyses and comparisons of interventions or population subgroups were not meaningful, because of the small number of studies that resulted in small subgroup sizes.

3.2 Results of the attendance at the exercise interventions (BENEFIT study)

During the recruitment period of the BENEFIT study beginning in December 2015 until its completion end of October 2022, 952 eligible patients were identified (Figure 11), of which a total of 63 patients were never contacted, mainly because of wrong contact information (N=40).

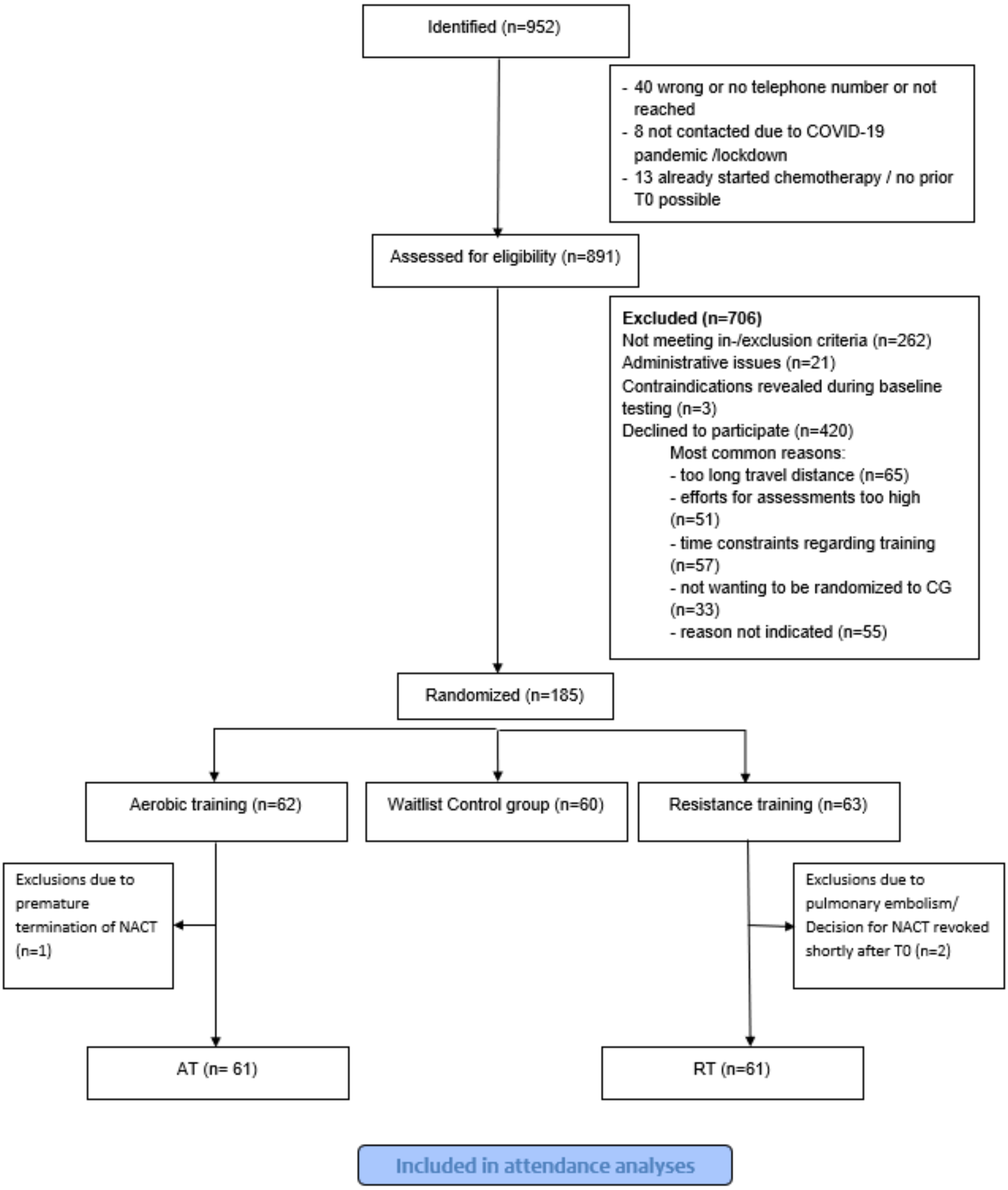


Figure 11: Flowchart of the BENEFIT-patients included in the attendance analyses

3.2.1 Study population included in the attendance analyses

After excluding four patients (without randomization: 1, AT: 1, RT: 2) due to medical reasons, the remaining 122 BENEFIT patients (AT: 61, RT: 61) that exercised during the neoadjuvant chemotherapy were included in the analyses. The attendance of 7 patients (AT: 3, RT: 4) was set to zero, because they never started their supervised training at the training facility.

The mean age of all patients who were randomized to either AT or RT was 50.1 (± 11.1) years and a BMI of 25.6 (± 5.1) kg/m^2. The majority was married or living with a partner (78.3%), had one (25.0%) or two (39.2%) children and were on sick leave (67.8%). Slightly more than half of all patients (57.4%) had a university or high school degree.

Table 8: Characteristics of the patients included in the attendance analyses, adopted from (Goldschmidt et al. 2024b)

Variable		**AT**		**RT**		
		M	*SD*	*M*	*SD*	*p*
Age		51.7	11.4	48.6	10.7	0.13
Body mass index		25.7	5.9	25.6	4.1	0.94
		N	*%*	*N*	*%*	*p*
Marital status						
	Married/living with a partner	47	77.1	47	79.7	0.73
	Living alone	14	23.0	12	20.3	
Having children < 18 years		19	31.2	25	42.4	0.21
Currently employed						
Education	University degree	25	41.0	24	40.0	0.70
	High school graduation	13	21.7	8	13.3	
	Lower	23	38.3	28	46.7	
Experience with resistance training		33	54.1	32	54.2	0.99
Exercise in youth		44	72.1	43	70.5	0.84
		Median MET-h	*Q1-Q3*	*Median MET-h*	*Q1-Q3*	*p*
Physical activity behavior 12 months prior to study [median MET-h, Q1-Q3]	Walking	4.3	1.6-10.4	7.4	3.2-15.0	0.04
	Cycling	0.7	0.0-4.0	0.9	0.0-6.1	0.78
	Sports	0.9	0.0-3.9	1.2	0.0-4.5	0.84
		M	*SD*	*M*	*SD*	*p*
Fatigue		32.5	24.0	33.9	21.4	0.72
Pain	No	12	20.0	25	41.0	0.94
	Mild	16	26.7	10	16.4	
	Moderate	13	21.7	6	9.8	
	Severe	16	26.7	16	26.2	
Nausea		16.4	18.2	14.6	19.7	0.62
Perceived social support		93.7	15.4	91.4	13.8	0.40

AT: Aerobic exercise training; M: Mean; MET-h: Metabolic equivalent of task in hours per week RT: Resistance exercise training; SD: Standard deviation; Q1: first quartile; Q3: third quartile

3.2.2 Individual exercise attendance

The patients attended on average (± SD) 44.1% (± 29.3%) of the prescribed exercise interventions. Stratified by arm, the attendance was 45.2% (± 29.7%) for AT and 43.0% (± 29.1%) for RT with no significant group differences (*p* > 0.05) (Figure 12).

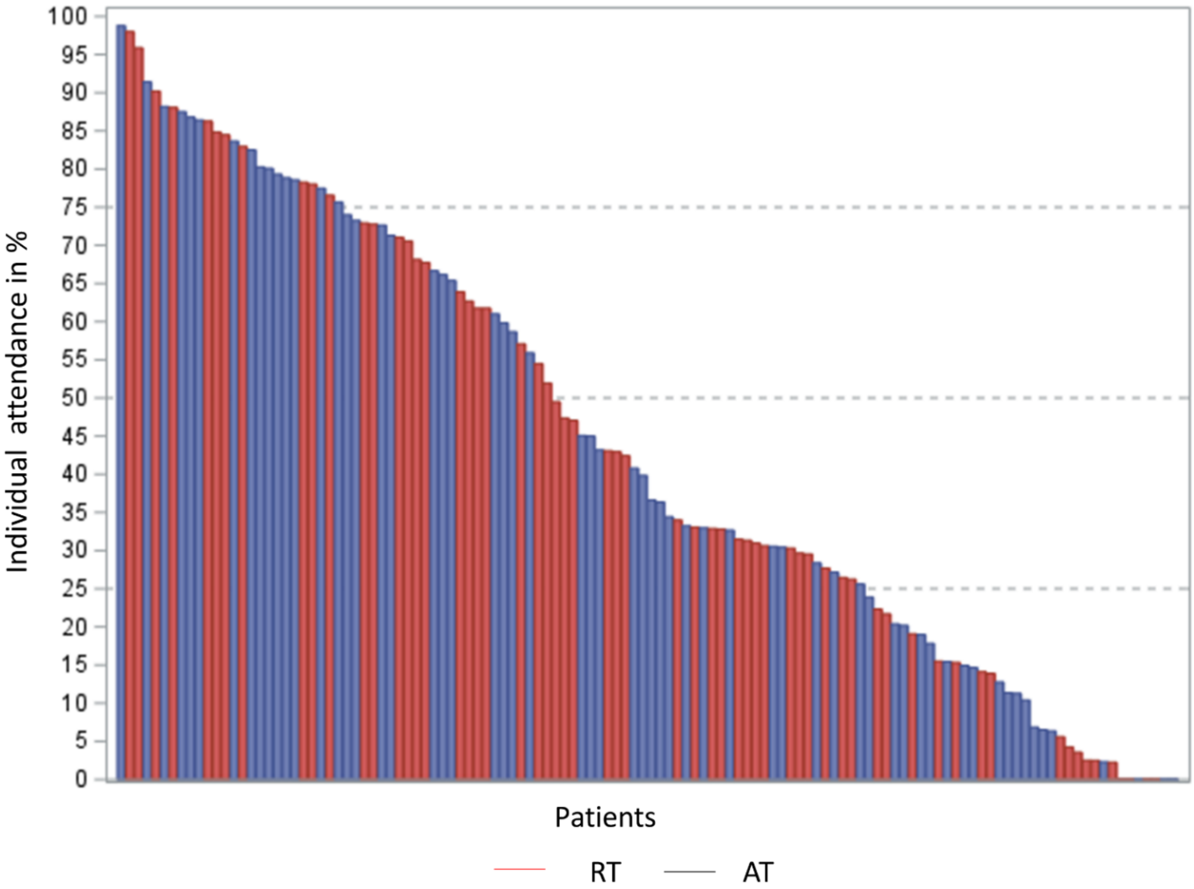


Figure 12: Waterfall plot of the individual attendance at the supervised exercise sessions in the training facility (Goldschmidt et al. 2024b)

With only 50 patients (41.3%) attending >= 50% of all supervised exercise sessions, the majority of patients attended less than 50% of all prescribed supervised exercise sessions.

3.2.3 Group attendance per week of training

The exercise attendance may change over time, dependent on the received treatment and, thus, particularly the weekly attendance at the exercise sessions during the neoadjuvant chemotherapy may reveal an insight into the treatment regimen as potential influencing factor for the overall low attendance rate. The attendance rate stratified by the received intervention is presented in Figure 13.

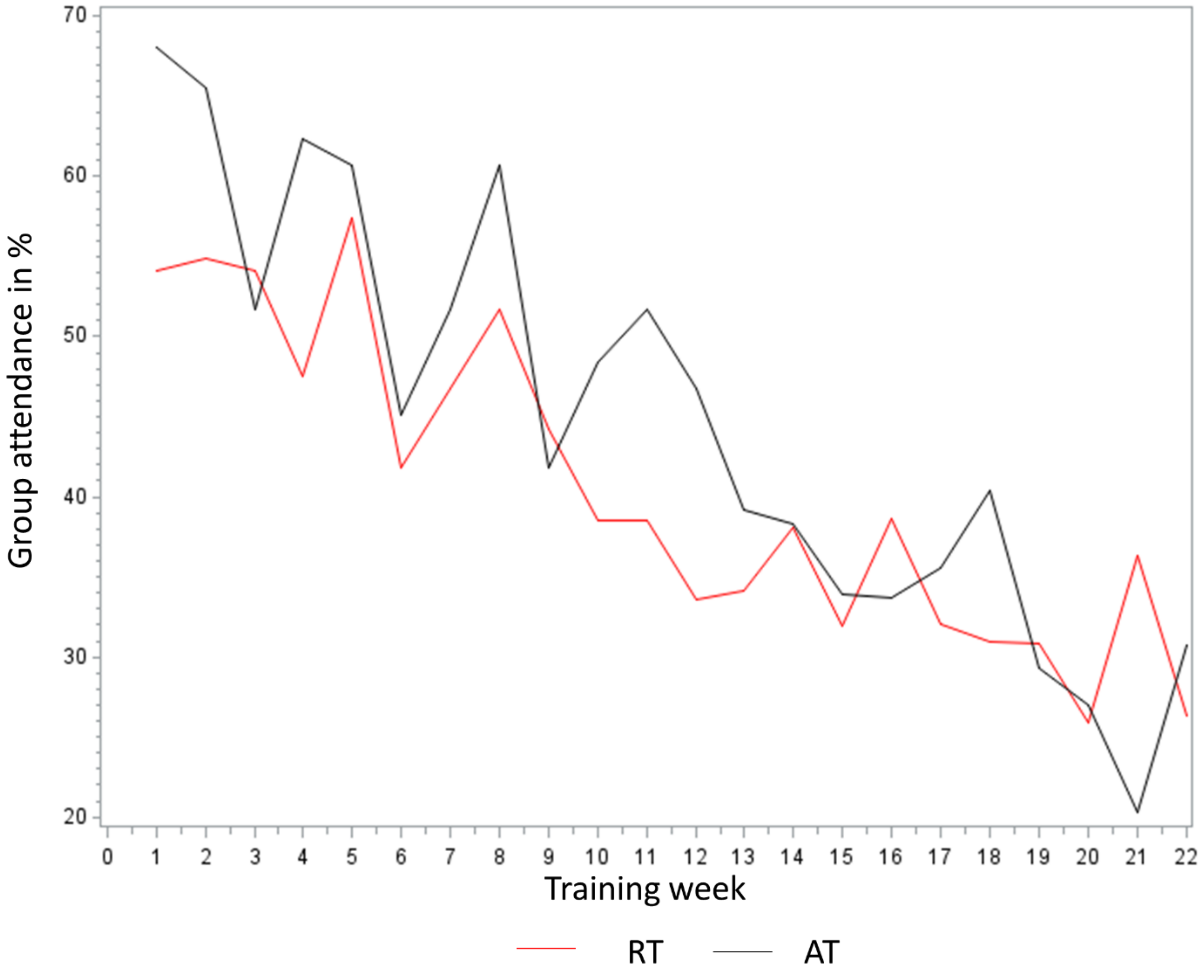


Figure 13: Weekly attendance at the exercise sessions (Goldschmidt et al. 2024b)

The *mean* (± *SD*) attendance at the weekly prescribed supervised exercise sessions was 41.8% (±12.1%; AT: 43.4% (± 14.3%), RT: 40.3% (± 9.4%)). The groups did not statistically significantly differ from each other ($p > 0.05$).

3.2.4 Factors influencing the individual exercise attendance

Multiple regression analyses were conducted to assess the association of possible influencing factors with the attendance at the exercise interventions. For this purpose, the PRO assessed mid-intervention via questionnaires, the socio-demographics assessed at baseline and the distance to the training facility were taken into consideration. The results of the multiple regression analyses are displayed in Table 9.

Table 9: Possible determinants of the exercise attendance, adopted from (Goldschmidt et al. 2024b)

Variable		Beta-Estimate	Standard Error	Two-sided p-value
Group	Aerobic exercise training		Reference	
	Resistance exercise training	-1.50	4.75	0.75
Age		0.31	0.21	0.14
Body mass index		-1.68	0.48	0.0007
Marital status	Married/living with a partner		Reference	
	Living alone	-16.35	5.92	0.007
Education	University degree		Reference	
	High school graduation	-23.59	6.56	0.0005
	Lower	-0.51	5.17	0.92
Fatigue		-0.006	0.12	0.96
Pain	No		Reference	
	Mild	1.96	6.58	0.77
	Moderate	-3.57	7.28	0.63
	Severe	-12.07	7.71	0.12
Nausea	No		Reference	
	Yes	-14.57	5.26	0.007

Table 9 (continued)

Variable		**Beta-Estimate**	**Standard Error**	**Two-sided p-value**
Physical activity and exercise behavior	Walking	-6.21	2.22	0.006
	Cycling	-2.10	2.03	0.30
	Sports	2.41	2.03	0.24
Patients' rating of the exercise	'good' or 'very good'		Reference	
	'very poor', 'poor', 'OK'	-21.78	7.33	0.004

The attendance was higher in partnered (*ß* = 16.35; *p* = 0.007) patients, who graduated from university (*ß* = 23.58; *p* = 0.0005), had a lower BMI (*ß* = 1.68; *p* = 0.0007), who walked less in the 12 months prior diagnosis (*ß* = 6.21; *p* = 0.006), rated their exercise intervention as 'good'/'very good' (*ß* = 21.78; *p* = 0.004) and did not experience nausea (*ß* =14.57; *p* = 0.007; Figure 14) or pain (*ß* = 12.07; *p* = 0.12).

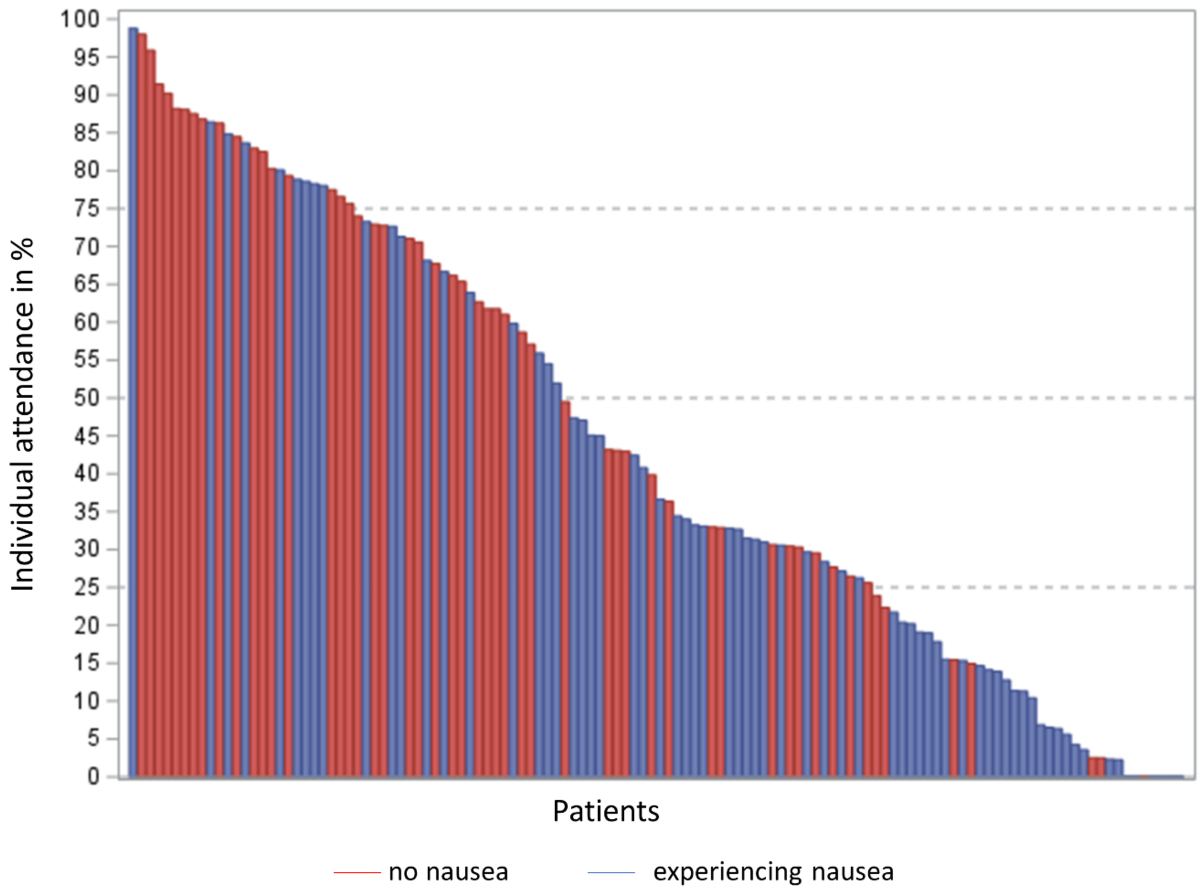


Figure 14: Individual attendance at the exercise sessions stratified by experiencing (no) nausea (Goldschmidt et al. 2024b)

Patients who liked their intervention and, therefore, rated it as ‘good’ or ‘very good’ attended statistically significantly more exercise sessions than the patients, who rated their intervention as ‘poor’ or ‘very poor’ (*ß* = 21.78; *p* = 0.004). But interestingly, no statistically significant association between having received the exercise intervention the patient would have preferably chosen at baseline (*ß*=6.91; *p* = 0.24) could be observed. However, it needs to be noted that the exercise preferences were only available for 91 (74.6%), thus not all patients. Slightly more than half of the patients (N=63; 51.6%) received the intervention, they would have preferably chosen at baseline, if they would have been able to choose. Most of the patients would have preferably chosen training during the neoadjuvant chemotherapy irrespective of the type of training: training in general (26.4%), AT (27.5%) or RT (27.5%). Just 9.9% would have chosen the exercise after the surgery and 8.8% had no preferences.

No variable was observed to have any confounding effect on any variable included in the model.

3.3 Maintenance of an aerobic or resistance training after end of intervention (BENEFIT study)

Subsequent to the aforementioned meta-analyses regarding (general) PA behavior after exercise interventions, the exercise maintenance after interventions, i.e., how many and for how long participants maintain the training of the intervention after end of intervention, and determinants and patient-reported reasons for maintenance or discontinuation of the training were investigated more specifically. For these analyses, the data of the BENEFIT study were used.

3.3.1 Study population included in the maintenance analyses

The maintenance of a training after completing an exercise intervention requires a certain training frequency. For the subsequent analyses, the training frequency was set to a participation in ≥ 7 exercise sessions. If the patients attended only up to 6 exercise sessions, they were excluded from the analyses, because this training attendance would then either represent a rather sporadic training or a training discontinuation within the first three weeks of the training intervention. Thus, of all 119 (64.7%) BENEFIT-patients, who had yet completed at least one follow-up measurement after the intervention period (AT: 39 of 61, RT: 40 of 62, CG: 40 of 60), 18 patients had to be excluded from the analyses due to a low exercise attendance (AT: 6, RT: 7, CG: 4; Figure 15). A total of 20 patients, all of the CG group, never began their training intervention. The reported reasons for not starting an exercise intervention were ‘no specific reason provided or not reported (N=10)’, due to the ‘Covid-19 pandemic (N=4)’, ‘death (N=2)’, ‘disease progress (N=2)’ and ‘experiencing too severe therapy-related side-effects (N=2)’.

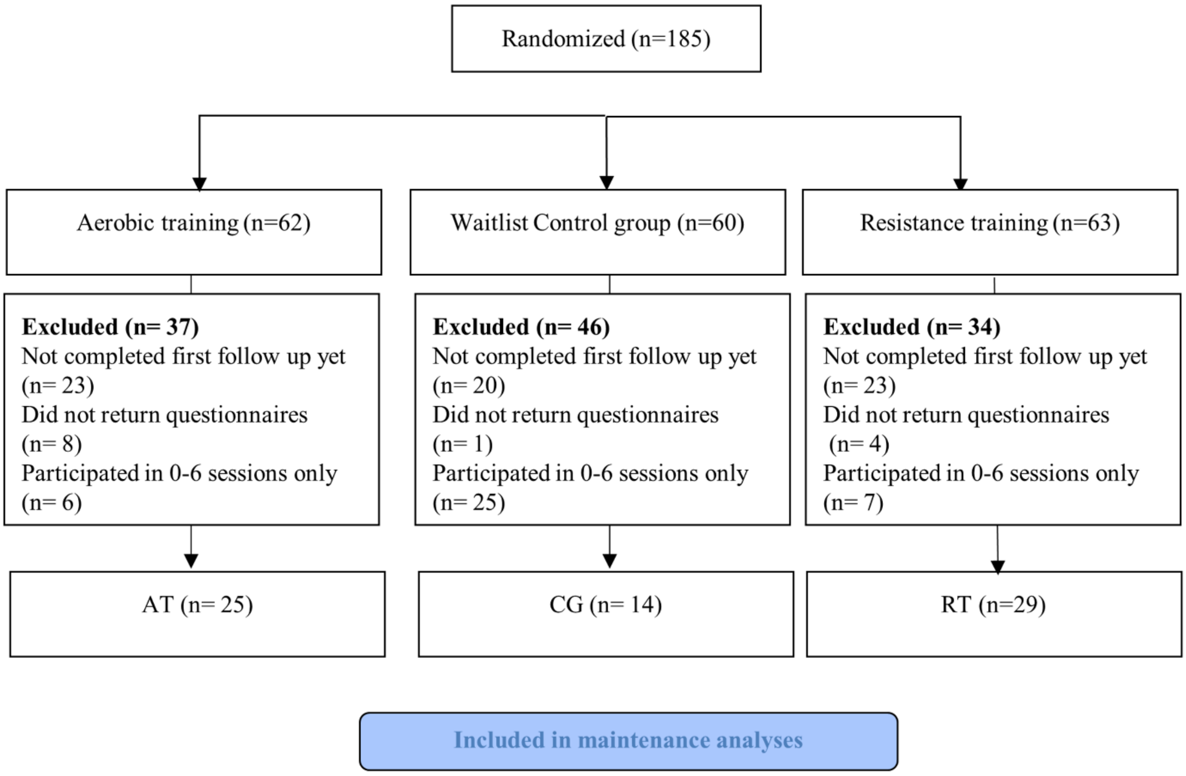


Figure 15: Flowchart of the BENEFIT-patients included in the maintenance analyses

Thus, the data of 82 patients (AT: 33, RT: 33, CG: 16), who completed at least one questionnaire post-intervention, could be included in the analyses. Unfortunately, 14 patients (AT: 8, RT: 4, CG: 2) did not return their questionnaires (hereafter referred to as non-participants), even upon reminder. So, overall the data of 68 patients (hereafter referred to as participants) could be analyzed (AT: 25, RT: 29, CG: 14). The baseline characteristics of the participants and the non-participants are summarized in Table 10.

Table 10: Baseline-characteristics of the participants with ≥ 7 training sessions and non-participants with < 7 training sessions that completed at least one follow-up questionnaire, adopted from (Goldschmidt et al. 2024a)

	Participants (N=68)		Non-participants (N=14)		Two-sided p-value
Age, mean (SD)	52.2	10.5	49.0	9.2	0.31
Body mass index, mean (SD)	26.1	5.2	27.8	9.3	1.00
Married/living with partner, N (%)	57	83.8	10	71.4	0.28
Having children < 18 years, N (%)	23	33.8	6	42.9	0.52
Currently employed, N (%)	16	23.5	5	35.7	0.34
Higher level of education, N (%)	36	52.9	2	14.3	0.01
Health related quality of life, mean (SD)	68.1	17.2	67.3	21.1	0.88
Total amount of walking [MET-h per week], Median (Q1, Q3)	5.2	1.8, 10.2	6.6	0.7, 1.1	0.97
Total amount of cycling [MET-h per week], Median (Q1, Q3)	0.3	0.0, 2.7	3.2	0.9, 4.8	0.01
Total amount of sports [MET-h per week], Median (Q1, Q3)	1.5	0.0,6.0	0.0	0.0, 3.5	0.18

N: Number of participants; SD: Standard deviation; Q1: first quartile; Q3: third quartile
** Non-participants: All eligible patients who did not returned the questionnaires on training continuation*

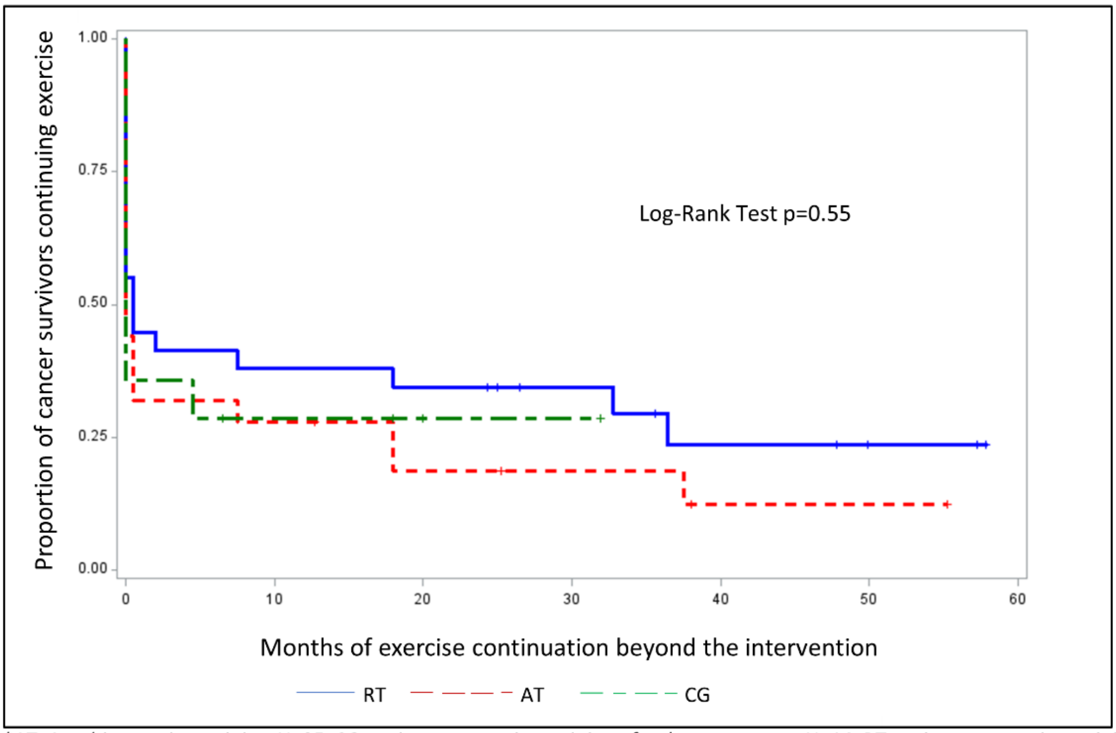
The participants were slightly older than the non-participants with an average age of 52.2 (± 10.5) years and had a slightly lower BMI of 26.1 (± 5.2) kg/m^2. The majority of participants (83.8%) and non-participants (71.4%) were partnered or married and had one or two children (participants: 83.6%, non-participants: 57.1%). Of the 61 patients, who reported at baseline not to work, 40 participants and 8 non-participants were on sick leave.

Comparing the participants with the non-participants, there were significant differences regarding the education, with statistically significant more patients having a university or high school degree compared to the non-participants (p = 0.01). It needs to be noted that there were 68 participants and only 14 non-participants. But, besides these differences in the number of patients per group, the non-participants statistically significantly have on median spent a higher amount with cycling (*p* = 0.01).

3.3.2 Frequency and duration of maintaining the training after end of intervention

Of the 68 eligible patients included in the analyses, 32 (AT: 11, RT: 16, CG: 5) continued their exercise intervention after completing the study intervention phase for a median duration of 19.0 months (first quartile- Q1: 5.5 months, third quartile- Q3: 36.0 months).

Comparing the three groups, the participants that were randomized to the RT group continued their training longer than those who received AT or CG, but the difference was not statistically significant (Kruskal-Wallis test p = 0.53; Figure 16). The median time of continuing the exercise intervention beyond the intervention phase was 25.8 months (Q1, Q3: 4.8, 42.1) for RT, 18.0 months (0.5, 37.5) for AT and 17.9 months (6.5, 20.0) for CG. Also, more participants of the RT-group continued their training compared to both of the other groups (log-rank p = 0.55). Comparing AT and RT as the groups, who exercised during the neoadjuvant chemotherapy, no statistically significant difference could be observed (log-rank p = 0.29; Figure 16).



**AT: Aerobic exercise training-N=25; CG: resistance exercise training after breast surgery-N=14; RT: resistance exercise training-N= 29*

Figure 16: Kaplan Meier Analysis of the exercise maintenance after the intervention phase, stratified by randomization group (Goldschmidt et al. 2024a)

Of the patients, who initially continued the training after completing the exercise intervention phase, 16 (AT: 7, RT: 8, CG: 1) stopped their exercise on median 6 months (Q1, Q3: 0.5, 18) after completing the intervention. The groups did not statistically significantly differ with RT quitting after a median 4.8 months (Q1, Q3: 0.5, 25.4), 7.5 months (0.5, 18) for AT and CG: 4.5 months (4.5, 4.5); Kruskal-Wallis test $p = 0.99$.

With 36 patients (AT: 14, RT: 13, CG: 9) who stopped the intervention immediately after completing the intervention phase, slightly more than half of the investigated patients (52.9%) reported not to maintain their randomized exercise beyond the intervention phase. The proportion of patients, who discontinued the exercise intervention immediately, varied between the three groups, with most patients belonging to CG, but no statistically significant differences between the groups could be observed (RT: 44.8%, AT: 56.0%, CG: 64.3%, Fisher's exact test: $p = 0.49$).

3.3.3 Reasons for maintenance or discontinuation

The most frequent three reasons the patients reported for continuing their exercise were physical well-being (81.3%), psychological well-being (71.9%) and having a better feeling after exercising (46.9%; Table 11). Additionally, the patients were asked to indicate their three main reasons for training (dis-)continuation ranked according to their importance. The Top 1 reason to continue the training of the exercise intervention was physical well-being (50%), the Top 2 reasons was psychological well-being (40.6%), and the Top 3 reason was feeling better after exercising (23.3%). There were no substantial differences between the groups.

Table 11: The patients' reported reasons to maintain the exercise intervention beyond completion of the study intervention phase (Goldschmidt et al. 2024a)

Reasons to maintain the exercise beyond the study intervention phase	Total (N=32)		RT (N=16)		AT (N=11)		CG (N=5)	
	N	%	N	%	N	%	N	%
Physical well-being, improve performance	26	81.3	15	93.8	6	54.5	5	100.0
Psychological well-being	23	71.9	13	81.3	7	63.6	3	60.0
I feel better after the exercise	15	46.9	8	50.0	4	36.4	3	60.0
I enjoy the exercise	11	34.4	7	43.8	3	27.3	1	20.0
Reducing risk of recurrence/metastases	8	25.0	3	18.8	4	36.4	1	20.0
Exercise is good for the health	4	12.5	1	6.3	2	18.2	1	20.0
Personal contact with others are important	1	3.1	1	6.3	0	0.0	0	0.0
Supervision through trainer is important to me	1	3.1	0	0.0	0	0.0	1	20.0
My health care professional advised me to do it	1	3.1	1	6.3	0	0.0	0	0.0
Motivated to stay healthy	1	3.1	1	6.3	0	0.0	0	0.0
My family or friends advised me to do it	0	0.0	0	0.0	0	0.0	0	0.0

AT: Aerobic exercise training; CG: Resistance exercise training after the breast surgery; RT: Resistance exercise training

The 16 patients who continued their training for some time beyond the intervention phase reported physical well-being (50%), psychological well-being (31.3%) and having a better feeling after exercising (31.3%; Table 12) as reason most frequently before they discontinued it. The three main, i.e., Top 3 most important reasons to maintain the exercise were physical well-being (25.0%) and reducing the risk of recurrence/metastases (25.0%) as Top 1 reasons, the second most important reason was psychological well-being (31.3%) and marked as Top 3 was physical well-being (31.3%).

Table 12: The patients' reported reasons to maintain the exercise intervention beyond completion of the study intervention phase before discontinuing it at a later timepoint (Goldschmidt et al. 2024a)

Reasons to maintain the exercise intervention beyond the study intervention phase before discontinuing it at a later timepoint	Total (N=16)		RT (N=8)		AT (N=7)		CG (N=1)	
	N	%	N	%	N	%	N	%
Physical well-being, improve performance	12	75.0	8	100.0	3	42.9	1	100.0
Psychological well-being	9	56.3	5	62.5	4	57.1	0	0.0
I feel better after the exercise	8	50.0	5	62.5	2	28.6	1	100.0
Reducing risk of recurrence/metastases	4	25.0	2	25.0	2	28.6	0	0.0
I enjoy the exercise	3	18.8	2	25.0	1	14.3	0	0.0
Exercise is good for the health	2	12.5	0	0.0	2	28.6	0	0.0
Supervision through trainer is important to me	1	6.3	0	0.0	0	0.0	1	100.0
My health care professional advised me to do it	1	6.3	1	12.5	0	0.0	0	0.0
Motivated to stay healthy	1	6.3	1	12.5	0	0.0	0	0.0
Personal contact with others are important	0	0.0	0	0.0	0	0.0	0	0.0
My family or friends advised me to do it	0	0.0	0	0.0	0	0.0	0	0.0

AT: Aerobic exercise training; CG: Resistance exercise training after the breast surgery; RT: Resistance exercise training

The 16 patients who continued their training for some time beyond the intervention phase before discontinuing it, reported most frequently a lack of time (43.8%), having a long travel distance to the training location (43.8%) and the then ongoing Covid-19 pandemic (37.5%; Table 13) as most frequent reason to discontinue the training. The three most important reasons for discontinuing their exercise intervention after previously maintaining it for some time beyond the completion of the intervention phase was a lack of time (31.3%) as Top1 reason, the high exercise-related costs (18.8%) and a too long travel distance to the training location (18.8%) as Top2 reasons.

Table 13: The patients' reported reasons to discontinue the exercise intervention at a later timepoint (Goldschmidt et al. 2024a)

Reasons to discontinue the exercise intervention at a later timepoint	Total (N=16)		RT (N=8)		AT (N=7)		CG (N=1)	
	N	%	N	%	N	%	N	%
No time	7	43.8	4	50.0	3	42.9	0	0.0
The distance to the training location is too long	7	43.8	3	37.5	3	42.9	1	100.0
Covid-19 pandemic	6	37.5	3	37.5	3	42.9	0	0.0
Too expensive	5	31.3	4	50.0	1	14.3	0	0.0
I perform a different type of sports now	3	18.8	1	12.5	2	28.6	0	0.0
No motivation	2	12.5	0	0.0	2	28.6	0	0.0
Unsatisfied with supervision through trainer	1	6.3	1	12.5	0	0.0	0	0.0
I don´t like the training location	1	6.3	0	0.0	1	14.3	0	0.0
I do not see the point of the exercise	1	6.3	0	0.0	1	14.3	0	0.0
I don´t like the exercise	0	0.0	0	0.0	0	0.0	0	0.0
I do not enjoy the exercise	0	0.0	0	0.0	0	0.0	0	0.0
I do not see any improvements	0	0.0	0	0.0	0	0.0	0	0.0
My health care professional advised me not to do it	0	0.0	0	0.0	0	0.0	0	0.0
My family and friends advised me not to do it	0	0.0	0	0.0	0	0.0	0	0.0
Health issues	0	0.0	0	0.0	0	0.0	0	0.0

AT: Aerobic exercise training; CG: Resistance exercise training after the breast surgery; RT: Resistance exercise training

The three main reasons reported for training discontinuation of patients, who firstly maintained the training for some time, but then discontinued it after some time and those, who immediately stopped the training after completing the exercise intervention, were alike with a lack of time (50.0%) and the long travel distance to the training location (38.9%) within the top three reported reasons, but the most reported reason to immediately discontinue the exercise intervention was the change to a different type of exercise (52.8%, Table 14). Thereby, the most common reported Top 1 reasons were the change to a different type of exercise (13.9%) and health issues (13.9%), the most frequent reported Top 2 reason was a lack of time (25.0%) and the change to a different type of exercise (18.8%) was also the most often reported Top 3 reason to immediately discontinue the exercise after completing the exercise intervention phase.

Table 14: The patients' reported reasons to discontinue the exercise intervention immediately after completing the exercise intervention (Goldschmidt et al. 2024a)

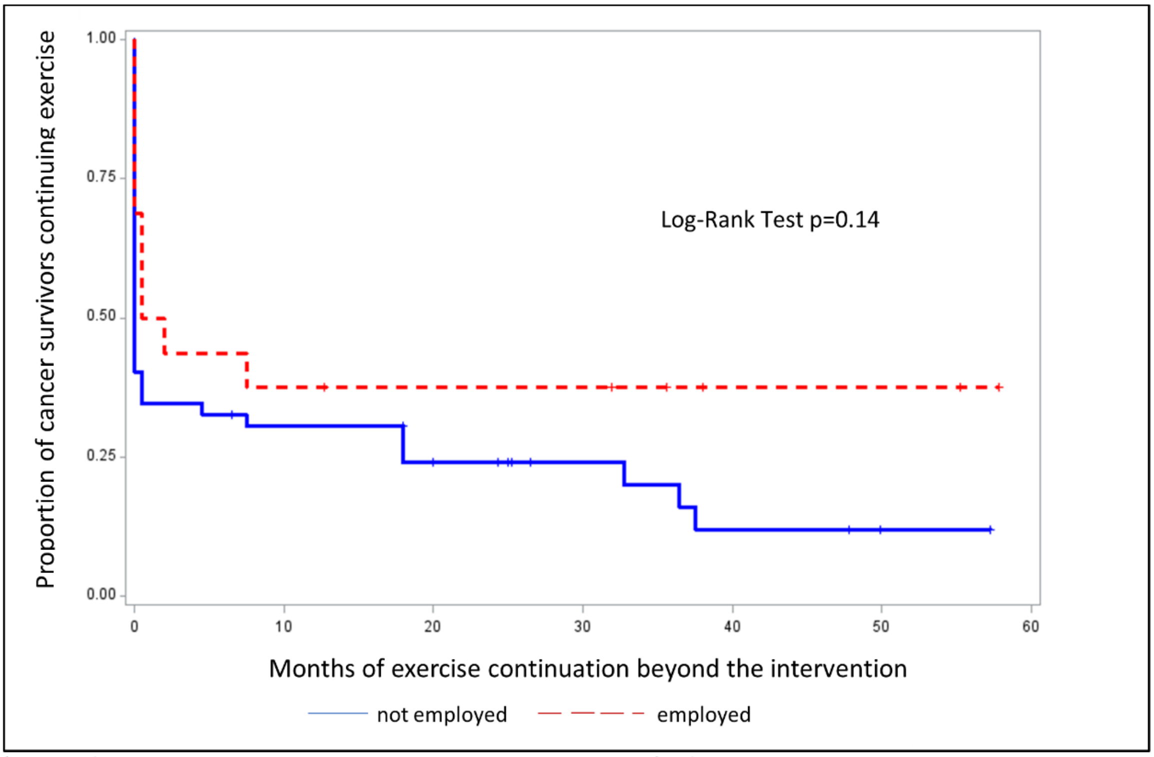
Reasons to discontinue the exercise immediately	Total (N=36)		RT (N=13)		AT (N=14)		CG (N=9)	
	N	%	N	%	N	%	N	%
I perform a different type of exercise now	19	52.8	6	46.2	9	64.3	4	44.4
No time	18	50.0	6	46.2	7	50.0	5	55.6
The distance to the training location is too long	14	38.9	3	23.1	6	42.9	5	55.6
Too expensive	8	22.2	3	23.1	2	14.3	3	33.3
I do not enjoy the exercise	7	19.4	3	23.1	4	28.6	0	0.0
Health issues	6	16.7	2	15.4	2	14.3	2	22.2
Covid-19 pandemic	5	13.9	2	15.4	1	7.1	2	22.2
No motivation	4	11.1	2	15.4	1	7.1	1	11.1
My health care professional advised me not to do it	2	5.6	2	15.4	0	0.0	0	0.0
Interaction/care of grand children	2	5.6	0	0.0	1	7.1	1	11.1
I don´t like the training location	1	2.8	0	0.0	0	0.0	1	11.1
Does not like gyms	1	2.8	1	7.7	0	0.0	0	0.0
Medical certification for exercise needed	1	2.8	0	0.0	0	0.0	1	11.1
The study intervention was completed	1	2.8	0	0.0	1	7.1	0	0.0
Unsatisfied with supervision through trainer	0	0.0	0	0.0	0	0.0	0	0.0
I don´t like the exercise	0	0.0	0	0.0	0	0.0	0	0.0
I do not see the point of the exercise	0	0.0	0	0.0	0	0.0	0	0.0
I do not see any improvements	0	0.0	0	0.0	0	0.0	0	0.0
My family and friends advised me not to do it	0	0.0	0	0.0	0	0.0	0	0.0

AT: Aerobic exercise training; CG: Resistance exercise training after the breast surgery; RT: Resistance exercise training

3.3.4 Factors influencing the exercise maintenance

By investigating possible influencing factors regarding the exercise maintenance associations between exercise maintenance and the socio-demographics as well as anthropometrics were observed.

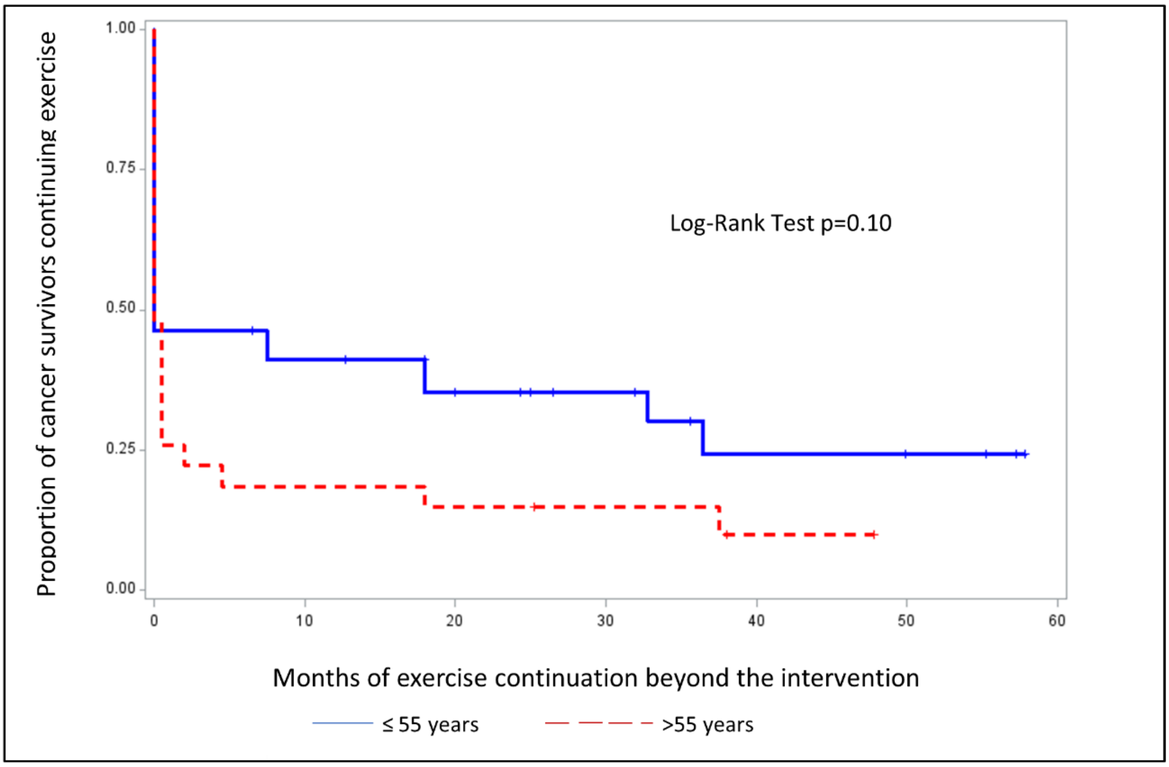
Thereby, being employed during the cancer therapy was associated with a longer time period, in which the exercise was maintained beyond the completion of the intervention phase (log-rank p = 0.14; Figure 17).



**AT: Aerobic exercise training-N=25; CG: resistance exercise training after breast surgery-N=14; RT: resistance exercise training N= 29*

Figure 17: Kaplan Meier Analysis of the exercise maintenance after the intervention phase, stratified by employment status (Goldschmidt et al. 2024a)

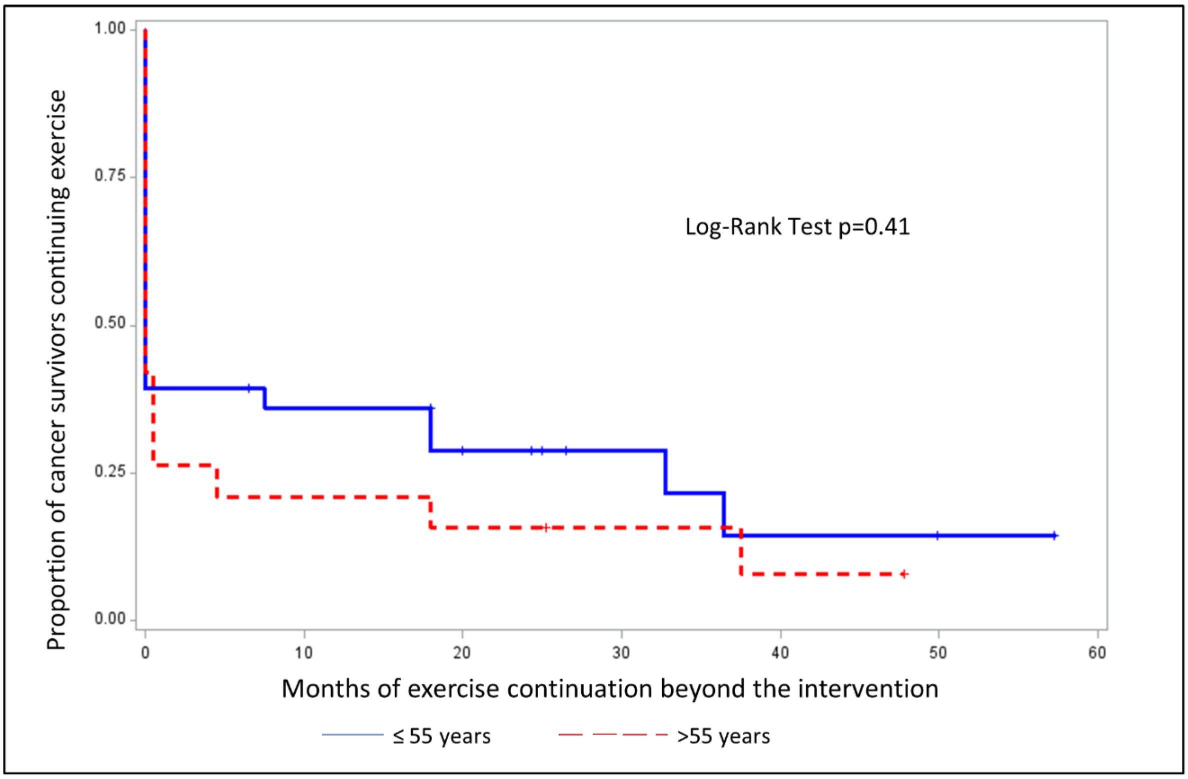
Patients ≤ 55 years of age maintained their exercise intervention longer beyond the intervention phase than the patients > 55 years (log-rank p = 0.10; Figure 18).



*≤ 55 years-*N=41; > 55 years=27*

Figure 18: Kaplan Meier Analysis of the exercise maintenance after the intervention phase, stratified by age (Goldschmidt et al. 2024a)

As younger patients (i.e., ≤ 55 years of age) may have children below the age of 18 years (i.e., underaged) which may impede the training continuation and simultaneously older patients (i.e., > 55 years of age) may have more time to exercise, two further Kaplan-Meier analyses were performed stratified by age in unemployed patients (Figure 19) and stratified by age and having underaged children (Figure 20).



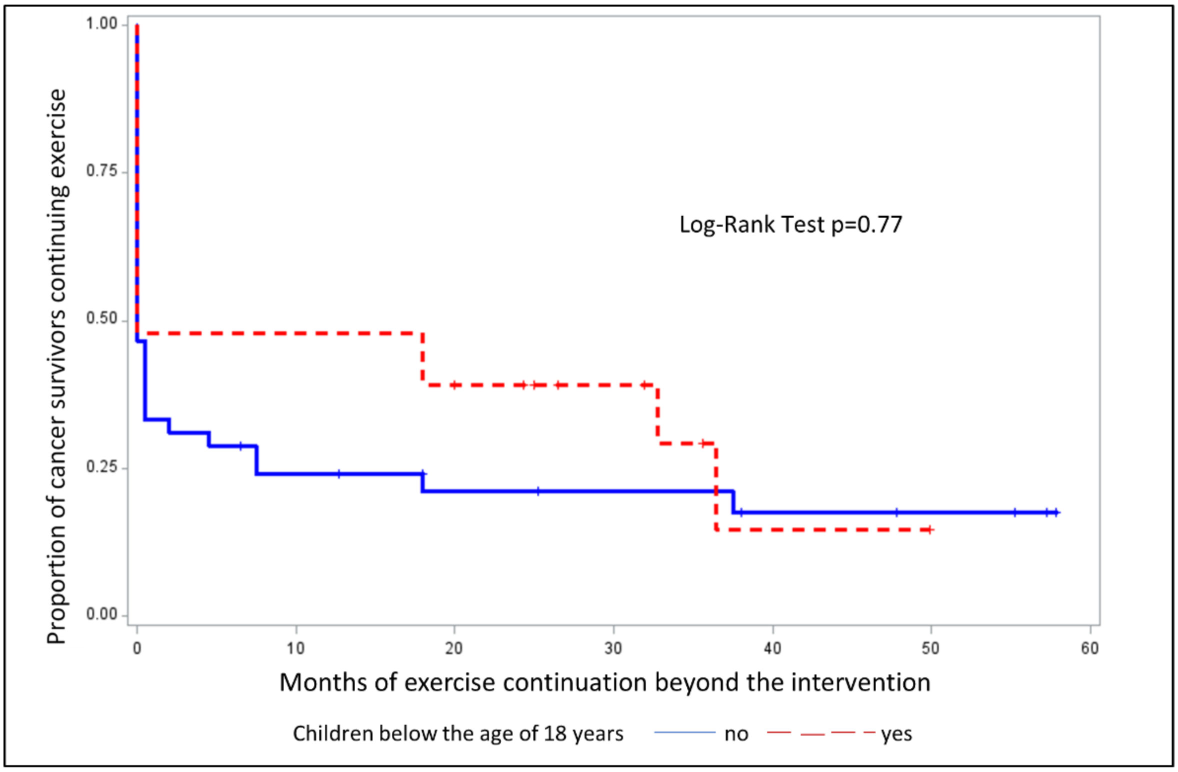
*≤ 55 years-*N=33; > 55 years=19*

Figure 19: Kaplan Meier Analysis of the exercise maintenance after the intervention phase, stratified by age of the patients, who were not employed at baseline (Goldschmidt et al. 2024a)

Considering only the patients, who were not employed during the cancer therapy (N=53), the association between the exercise maintenance in the younger compared to the older patients revealed that younger patients tend to maintain their training longer (log-rank p = 0.41). At least for the first three years after completing the intervention, just like it was observed in the overall sample.

The stratification of younger patients with underaged children revealed that more patients with children below the age of 18 years tended to maintain their randomized exercise for about 3 years beyond the intervention phase than those without underaged children (Figure 20).

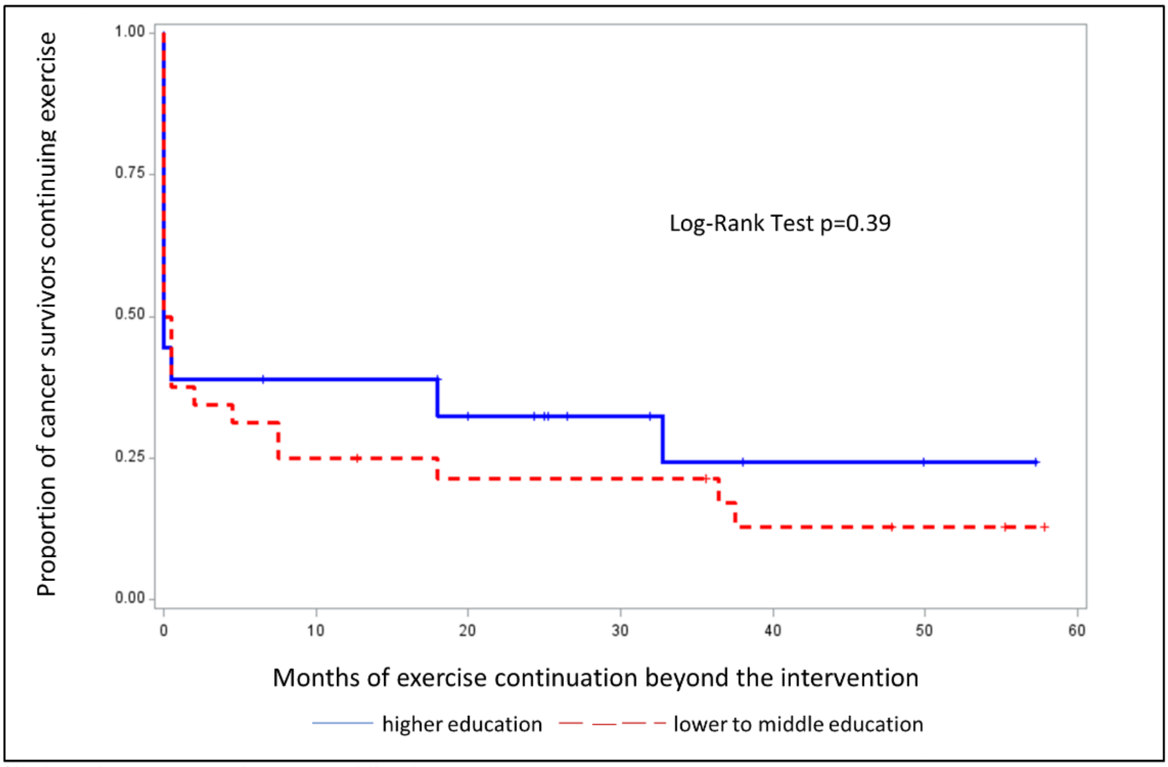
Thereafter it is comparable with only a slight superiority in the number of patients without children below the age of 18 years maintaining their exercise overall compared to patients with underaged children. They also maintained it about 10 months longer. The group differences were statistically not significant (log-rank p = 0.77).



**Having children below the age of 18 years: Yes-N=23; No-N=45*

Figure 20: Kaplan Meier Analysis of the exercise maintenance after the intervention phase, stratified by age of the patients, with and without underaged children (Goldschmidt et al. 2024a)

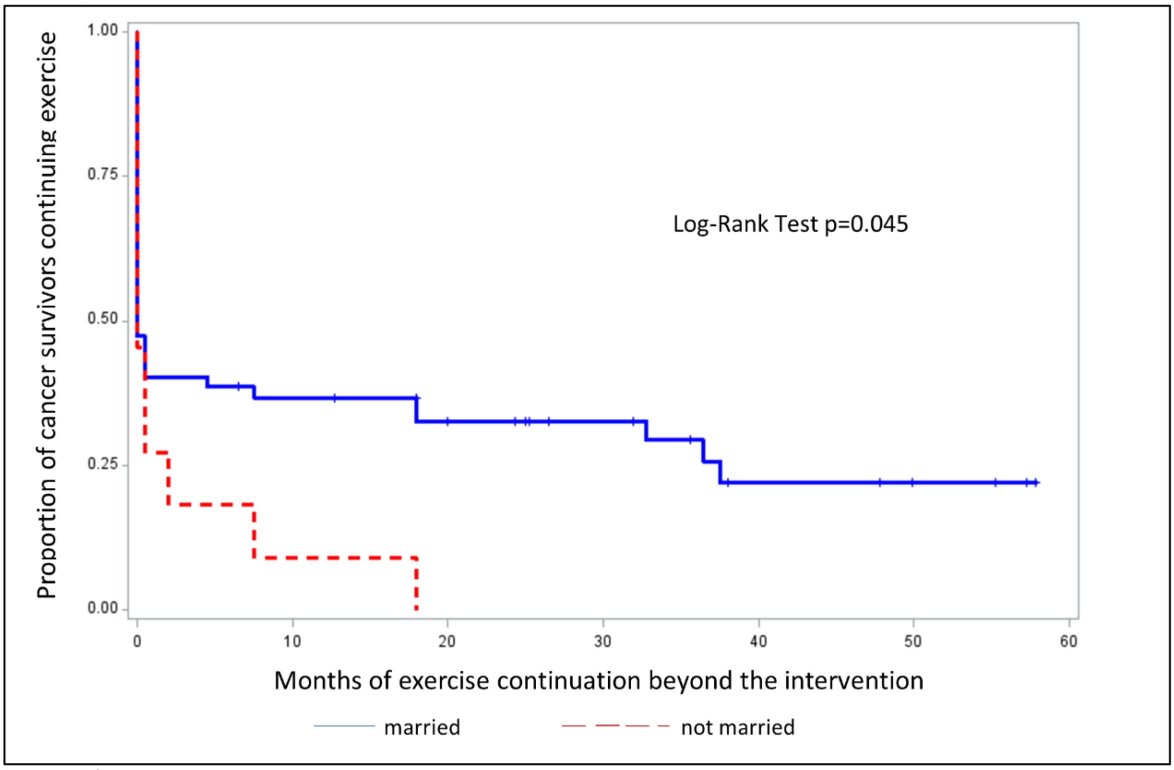
A statistically not significant association could be found between the level of education and exercise maintenance (log-rank p = 0.39; Figure 21). Descriptively, more patients with higher education maintained their exercise intervention. The duration of maintaining the exercise intervention beyond the intervention phase did not statically significantly differ between the groups.



**higher education-N=36; lower to middle education-N=32*

Figure 21: Kaplan Meier Analysis of the exercise maintenance after the intervention phase, stratified by level of education (Goldschmidt et al. 2024a)

A statistically significantly longer exercise maintenance could be observed among partnered patients compared to those without partners (log-rank p = 0.045, Figure 22). But there were 57 patients partnered compared to 11 unpartnered patients, of whom 1 was widowed.

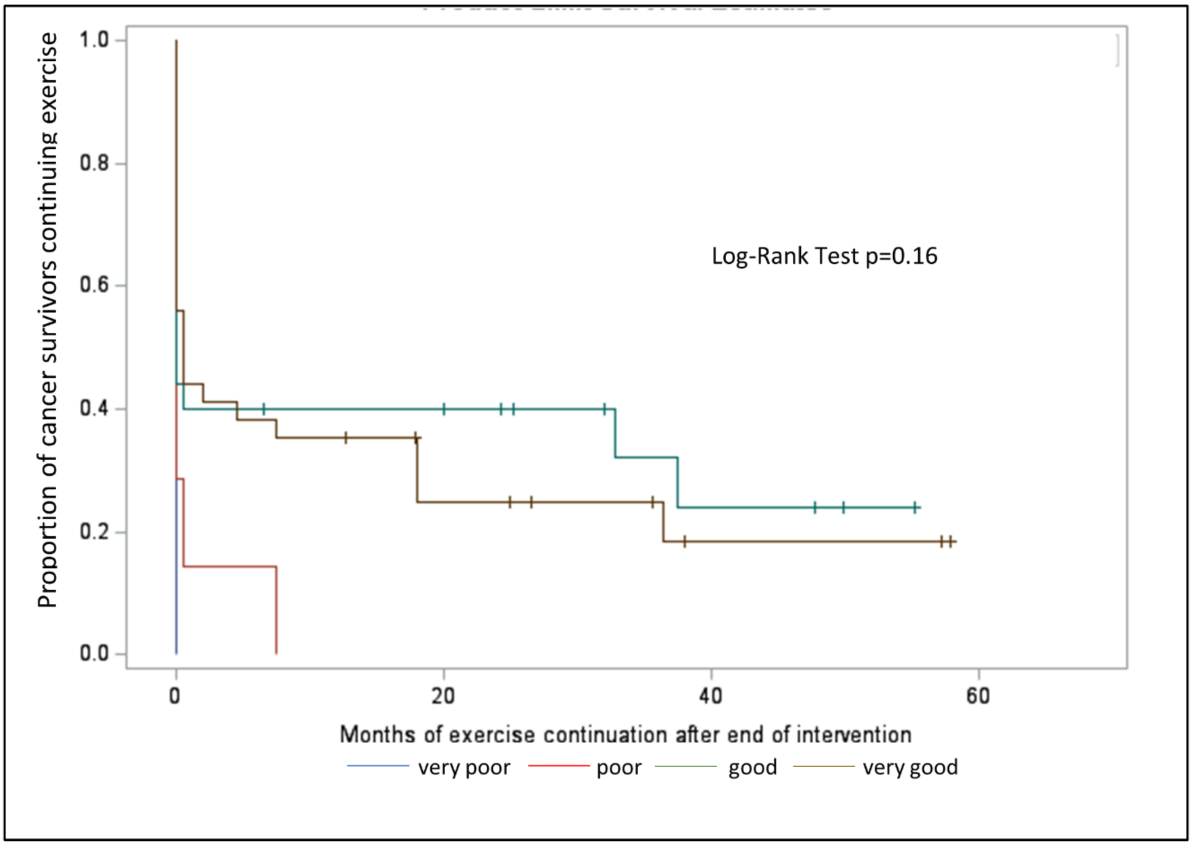


married/living with a partner=57; not married=11

Figure 22: Kaplan Meier Analysis of the exercise maintenance after the intervention phase, stratified by marital status (Goldschmidt et al. 2024a)

To assess if the patients' perception of the training may have an influence on the exercise maintenance overall and its duration, the patients' rating of the exercise intervention was investigated (Figure 23).

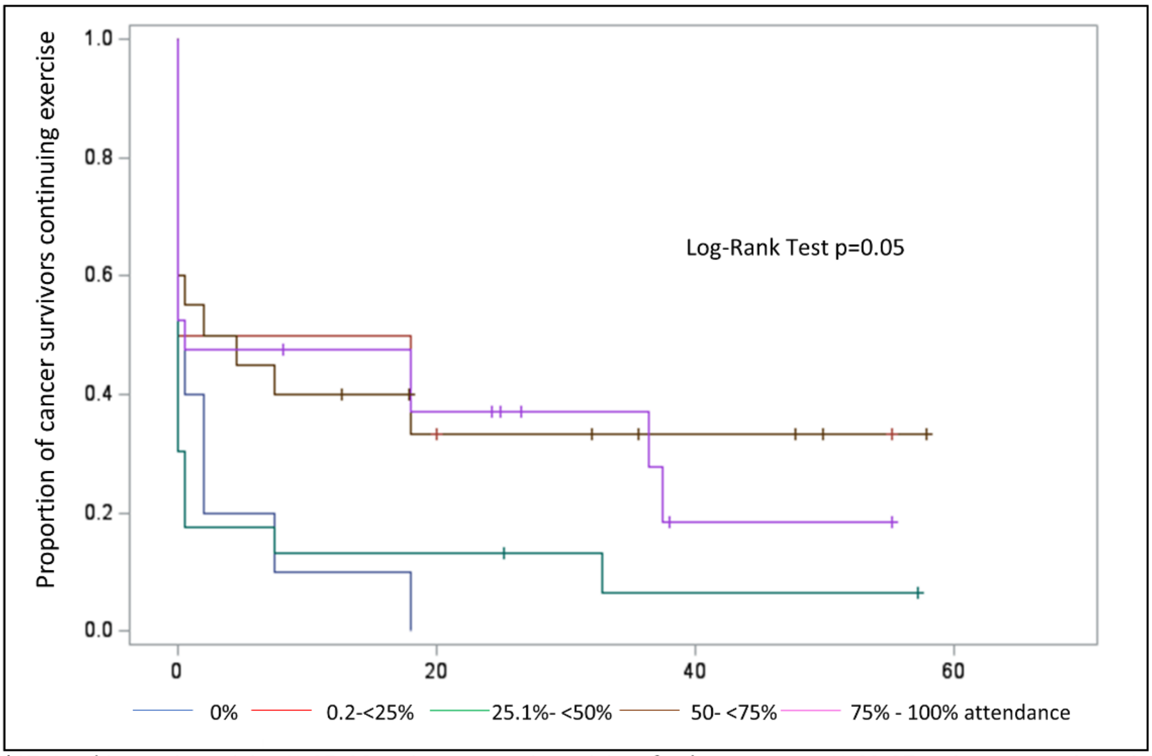
The patients, who rated their exercise intervention as 'very good' or 'good' maintained the exercise longer than the patients who rated their exercise as 'poor' or 'very poor'. The majority of patients (88.1%) perceived their intervention as 'very good' or 'good'. Comparing the patients, who received the exercise intervention during the neoadjuvant chemotherapy, RT had a slightly better rating than AT ('very good' / 'good': RT: 59% / 31% vs. AT: 40% / 44%). Not all patients, who rated their exercise intervention as 'good' or 'very good', maintained it beyond the intervention phase, but the proportion of patients, who discontinued it immediately with completing the intervention was statistically not significantly higher in patients who rated their exercise as 'poor' (63.0%) than those, who rated it as 'good' or 'very good' (37.0%; Chi^2 test: p = 0.057).



very poor : N=1, poor: N=7, good: N=25, very good: N=34

Figure 23: Kaplan Meier Analysis of the exercise maintenance after the intervention phase, stratified by the patient's rating of the received exercise intervention (Goldschmidt et al. 2024a)

To assess if the patients' exercise attendance might have an influence on the exercise maintenance overall and its duration, the attendance rate of all patients was investigated (Figure 24).



AT: Aerobic exercise training-N=27; CG: resistance exercise training after breast surgery-N=22; RT: resistance exercise training-N= 31

Figure 24: Kaplan Meier Analysis of the exercise maintenance after the intervention phase, stratified by the patient's exercise attendance

For comparisons, the attendance rate to the exercise sessions was grouped into '0%', '0 < 25%', '25% - <50%', '50% - <75%' and '75-100%'. The continuation time between these three groups did not statistically significantly differ from each other (Kruskal-Wallis test, Chi^2 test: $p = 0.27$). But, Kaplan-Meier analysis suggested that patients with low attendance at the exercise intervention tended to be less likely to continue the training after end of intervention (log-rank $p = 0.05$).

The patients who immediately discontinued their exercise intervention after the intervention phase tended to have a worse attendance at the exercise interventions (*median*: 49.5%, Q1: 33.0%, Q3: 76.6%) than the patients, who continued it for some months beyond the intervention phase before discontinuing it (*median*: 58.3%, Q1: 50.4%, Q3: 78.9%; Kruskal-Wallis test, Chi^2 test: $p = 0.055$). However, also patients with a higher attendance discontinued their training.

4 Discussion

The present thesis investigated attendance at exercise interventions and the influence of exercise interventions on the PA and PE behavior of breast cancer patients post-intervention. For this purpose, first a systematic review and meta-analyses were conducted on the influence of exercise interventions on the longer-term moderate to vigorous and total PA of breast cancer patients encompassing a follow-up period of several months up to several years after completing an exercise intervention (Goldschmidt et al. 2022). Further, the patterns and determinants of attendance at two different exercise interventions during neoadjuvant chemotherapy (Goldschmidt et al. 2024b) in an ongoing 3-arm randomized exercise intervention trial in breast cancer patients (BENEFIT study) were investigated. Finally, the maintenance of the training of the BENEFIT exercise interventions beyond its completion was investigated with regard to the proportion of patients, their reasons and the duration of maintaining their exercise intervention (Goldschmidt et al. 2024a).

The key findings can be summarized as follows:

1. The systematic review and meta-analyses showed that PA interventions could positively influence total and moderate-to-vigorous PA up to 60 months and 20 months, respectively, after completing the intervention phase.
2. The attendance of breast cancer patients during neoadjuvant chemotherapy at the aerobic or resistance exercise sessions in the BENEFIT study decreased with progressing duration of the chemotherapy.
3. Low attendance was significantly associated with higher BMI, lower education, not living with a partner, higher travel distance to the training facility, experiencing nausea or pain, worse patient’s rating of the exercise intervention, and a higher amount of walking in the 12 months prior to study start.
4. Attending either of the three BENEFIT interventions (i.e., AT or RT during the neoadjuvant chemotherapy or CG after the breast surgery) improved the exercise

behavior of the majority of the previously rather inactive breast cancer patients, partly up to 60 months post-intervention.

5. The training of a randomized aerobic or resistance exercise intervention was continued for a median of 19 months with no statistically significantly differences between AT, RT, or CG.
6. Main reasons to discontinue the training of the exercise intervention were the change to a different type of sport, a lack of time, and the long travel distance to the training facility.
7. Longer exercise maintenance was associated with younger age, being married/living with a partner and having a higher education.

The analyses and results of this thesis have been either published or accepted by journals. Thus, also parts of the discussion are close to these publications: (Goldschmidt et al. 2024b; Goldschmidt et al. 2024a; Goldschmidt et al. 2022).

4.1 Short- and long-term physical activity after exercise interventions - Systematic review and meta-analysis

The sustainability of exercise interventions on the longer-term total and moderate-to-vigorous PA of breast cancer patients was initially investigated with a systematic review and meta-analyses by considering (1) different types of PA (i.e., total PA, MVPA), (2) the mode of PA assessment (i.e., subjective or objective), and (3) different intervention characteristics (i.e., supervised/unsupervised training).

The results of the systematic review and meta-analyses suggested a longer-term effect of exercise interventions on the PA behavior, which is of only very small effect size regarding total PA but of moderate effect size regarding MVPA. However, the effect seemed to diminish after about a year. Yet, sustainability varied between studies. These observations confirm the results of a previously conducted systematic review and meta-analysis that investigated the effect of exercise interventions and/or exercise behavior change interventions on the longer-term moderate-to-vigorous PA (Grimmett et al. 2019). According to this study, not only exercise interventions are effective in improving the MVPA, but also interventions that target the behavior change, i.e., by providing wearables, printed materials or phone counselling (Grimmett et al. 2019).

The sustainable effects of exercise interventions on the PA behavior several months or even years after completing the exercise intervention could be observed in various ways. Besides the overall higher levels of PA and exercise compared to baseline (Daley et al. 2007b; Foucaut et al. 2019; Hayes et al. 2013; Husebø et al. 2014; Møller et al. 2020), a higher proportion of patients met the generally acknowledged global aerobic and/or resistance exercise guidelines (An et al. 2020b; Husebø et al. 2014), or walked more steps a day (Mustian et al. 2009).

The smaller effects observed for total PA (compared to MVPA) could not be attributed to a certain mode of PA delivery (supervised/unsupervised, group-based/face-to-face) or PA assessment method, but may be related to the activities accounted within the total PA, which may include the training of the intervention phase, but also every other activity and exercise that was performed, like occupational activity. Especially mild intensity PA, which often comprises many irregular and varying activities, is more prone to recall bias and measurement errors. This may be less the case for the assessment of MVPA, which includes activities that might be better remembered such as working out in a gym or going for a run/ bike ride (more regular or also rather exceptional) exercise. There, the exercise interventions appeared to have a moderate effect on the MVPA up to 20 months beyond the exercise intervention phase that reached statistical significance 6 months after completion of the intervention.

These small to moderate effects that vanish over time may be influenced by various factors, like the small number and heterogeneity of the included studies that also led to inconclusive results in two previously conducted systematic reviews (Abdin et al. 2019; Spark et al. 2013). Another explanation for the vanishing effects may be the potential selection bias in exercise intervention studies, as mostly those patients who are already active or at least more interested in PE and PA are willing to participate (Foucaut et al. 2019). This may be reflected in higher attendance (Courneya et al. 2014a; Foucaut et al. 2019). The selection bias itself as well as being part of an exercise intervention study may also lead to an increase in PA in the CG during the intervention and/or follow-up period (Foucaut et al. 2019; Hayes et al. 2013; Husebø et al. 2014; Penttinen et al. 2019; van Waart et al. 2015). If the PA behavior of IG and CG increase, there may be no significant differences in the PA behavior to observe and, thus, no significant differences between IG and CG would then imply that there were no or only small effects of the exercise intervention on the PA level (Foucaut et al. 2019; Hayes et al. 2013; Husebø et al. 2014; Møller et al. 2020; Penttinen et al. 2019; van Waart et al. 2015). Thus, the effects of exercise intervention studies on the longer-term PA would vanish.

The risk of overreporting PA of patients in the questionnaires may not be avoidable, as there is yet no gold standard for assessing the time spent with PA. To assess PA besides the self-reported questionnaires, most often accelerometry is used. By using the accelerometry, the overreporting may be avoided, but it is susceptible to underreporting. The underreporting of accelerometry may arise because of its limitations to assess the correct intensity of every activity or the activity itself. The limitations may thereby include the inability to assess low-motion activities (e.g., cycling) or the material, which is not waterproof yet and may be, therefore, not used to assess swimming (Rogers et al. 2009). However, Rogers and colleagues (2015) observed higher PA and PE behavior measured with accelerometry than was self-reported by the patients in the questionnaires (Rogers et al. 2015). The comparison of subjective (i.e., self-reported questionnaires) with objective (i.e., accelerometry) assessment of PA and PE behavior did not reveal any conclusive differences (Rogers et al. 2009). It needs to be considered that only four studies identified in the systematic review used accelerometry to assess the PA and PE behavior, which does not allow to draw any clear conclusions.

The comparison of supervised versus unsupervised exercise interventions regarding the PA and PE behavior revealed mixed findings. This may be related to the small number of included studies. Additionally, several studies offered a mixed supervised and unsupervised exercise intervention. Supervised exercise interventions usually have larger effects on various PRO such as overall health-related QoL, fatigue, anxiety and depressive symptoms than unsupervised exercise interventions (Campbell et al. 2019). Supervised interventions are usually associated with a higher training adherence, probably due to the reinforcement, motivation and attention (Turner et al. 2018), thus, resulting in higher PA and PE levels over the course of the intervention. However, these effects may fade after completing the intervention phase, when the patients need to exercise on their own and, thus, may be lost in the transition (Pinto et al. 2008; Schmidt 2017).

A further, not negligible factor regarding maintenance of the training or general higher levels of PA after completing a study-derived exercise intervention, may be the timing of the intervention. Only few of the studies included in the systematic review performed the exercise intervention after cancer therapy, which limits investigations and comparisons regarding the timing of the intervention. The impact of an exercise intervention on training maintenance and longer-term PA might differ between intervention during or after completion of cancer therapy, because cancer treatment represents a special period in time, in which many patients are more motivated to engage in healthy behavior, including PA and PE, and additionally have more time because the majority of patients is on sick leave. Often patients return to their pre-diagnosis PA and PE behavior after they completed their therapy and return to their previous social and occupational lives, irrespective of their previous participation in an exercise intervention (Kampshoff et al. 2014; Schmidt 2017). Thus, if the patients were already inactive before they participated in an exercise intervention study, they became inactive again or if they were never active, remain inactive (Kampshoff et al. 2014; Schmidt 2017; Steindorf et al. 2020). Therefore, it is not only a crucial concern to support the uptake of PA and PE during the cancer therapy but also enable its maintenance through specialized offers for cancer survivors after completing their therapy.

Comparisons between an individual and group-based setting, different types of exercises (i.e., aerobic versus resistance versus combined training) or analyses regarding the influence of different intensities, patients or treatment characteristics on the PA behavior up to 60 months after end of intervention were not possible due to the small sample size of eligible studies included in the systematic review and meta-analyses. Yet, there are results indicating that the type of exercise in the context of an intervention may affect the type of exercise that is performed in the longer term after completing the exercise intervention. An RCT compared 3 interventions with different types of exercise with each other, a standard dose of aerobic exercise (here: 25 to 30 minutes of aerobic exercise) with a higher intensity of aerobic exercise (here: twice the standard dose) with a combined aerobic (here: twice the standard dose) and resistance exercise (An et al. 2020b). They observed that a significantly higher percentage of participants of the aerobic exercise group met the aerobic exercise guidelines at the 6- and 24-months follow-up compared to the combined exercise group (An et al. 2020b). More participants of the combined exercise group met the resistance guidelines at the 6- and 24-months follow-up than the aerobic exercise group (An et al. 2020b). Likewise, breast cancer patients randomized to a resistance exercise intervention performed more strength training at the 12-month follow-up compared to pre-diagnosis as well as compared to the relaxation control group (Schmidt 2017). The influence of aerobic exercise intensity was not found to have a statistically significant influence on the PA behavior up to 24 months beyond the intervention phase in one randomized controlled exercise intervention study that compared 25 to 30 minutes of aerobic exercise with the group that exercised twice as much (An et al. 2020b).

The influence of demographic and clinical characteristics on the training maintenance after completing the BENEFIT exercise interventions revealed that younger patients (≤ 55 years) with academic education, living with a partner and being employed during cancer treatment tended to be more likely to maintain the training beyond the intervention phase. However, these conclusions need to be interpreted with caution as they were drawn solely based on Kaplan-Meier analyses and were not investigated with any further statistical tests due the violation of the proportional hazard assumptions. The statistically non-significant association between demographics and the longer-term PA behavior would be in line with the review of Kampshoff and colleagues (2014) that identified 6 studies that investigated possible influencing factors of the exercise maintenance after exercise interventions, which also revealed no clear results (Kampshoff et al. 2014).

The presented small to moderate effects of exercise interventions on the longer-term total PA up to 60 months and MVPA up to 20 months after end of intervention reveal the necessity to find further approaches to increase the PA behavior on a long-term basis. Adding self-regulatory behavior change techniques, i.e., firstly setting a goal, reviewing the behavioral goals, monitoring oneself, planning the action and solving the problem to an exercise intervention in an additional face-to-face session, appeared to increase the proportion of patients who maintained the training of the exercise intervention up to the 12-month follow-up assessment intervention (Mazzoni et al. 2021). These effects were observed in a follow-up study of 301 cancer survivors, who attended a maximum of 9 face-to-face sessions that were related to the resistance exercise intervention and at the follow-up study visits 3- and 9-months post-intervention intervention (Mazzoni et al. 2021). Alike, a meta-analysis in cancer survivors (Finne et al. 2018) and a systematic review and meta-analysis in healthy inactive adults (Howlett et al. 2019) observed and, therefore, suggested that interventions that aim to increase the PA and PE behavior beyond the intervention phase may profit from the addition of behavior change techniques that correspond to the (social) learning theory, which uses e.g., rewards, prompts and graded tasks. Additionally, helpful in sustainably fostering the uptake and maintenance of PA and PE, were written messages and phone calls of peer mentors (Pinto et al. 2021). This enables the conclusion that an exercise intervention with additional behavioral, social, and cognitive components may be necessary to sustainably take up the recommended PA and PE and keep it up in the long-run. This needs to be further investigated in future studies. In this regard, wearables and eHealth offers may contribute to the uptake of PA and PE and its maintenance after completing the exercise intervention.

Another study investigating the addition of cognitive behavioral therapy to a physical training compared to solely physical training did not observe any statistically significant group differences in the longer-term PA and PE behavior after completing the intervention (May et al. 2009). However, both groups increased their PA and PE behavior during the intervention and kept it until the 12-month follow-up assessment (May et al. 2009). Group-based training may allow social interaction and the self-efficacy may be improved through the support of the group. So far, the effect of group dynamics on the PA and PE behavior of cancer survivors is not clear and requires further investigation to be able to make the best use of the underlying group dynamic strategies of group-based trainings (Leach et al. 2019b).

4.2 Attendance at exercise interventions during neoadjuvant chemotherapy

The benefits and safety of regularly performed PA and PE in form of a training that is performed over a time period of 12 weeks with 2-3 exercise sessions of at least moderate intensity is well acquainted (Campbell et al. 2019). However, the role of adherence to the exercise prescriptions or even the sole attendance to the exercise session was so far still unclear. The present thesis investigated the patterns and influencing factors of attendance at exercise interventions of breast cancer patients during neoadjuvant chemotherapy in a currently ongoing 3-arm randomized controlled exercise intervention study (BENEFIT study).

The mean individual attendance was 44.1% (±29%) with no significant differences between the RT and AT groups. Hereby, seven of the analyzed 122 patients were not able to start the training of their exercise intervention due to too severe side-effects. This attendance is lower than was reported in previously conducted exercise intervention studies with breast cancer patients undergoing chemotherapy, ranging from 63% to 82% (Bolam et al. 2019; Courneya et al. 2014a; Hornsby et al. 2014; Lund et al. 2019; van Waart et al. 2020). This may be due to the different cancer treatment regimens and the therewith related side-effects that may impede the attendance at exercise interventions. This would be in line with the study of Kirkham and colleagues (2020), who observed significantly higher attendance at a chemotherapy-periodized exercise (77% (±28%)) than under a standard linear exercise program (57% (±30%)) (Kirkham et al. 2020). The average attendance of the patients receiving a standard linear exercise prescription was with 57% (±30%) comparable to the attendance of the BENEFIT patients of 44% (±29%). Even though the patients in the BENEFIT study were allowed to adjust the exercise intensity according to their physical status, i.e., if they perceived it as too intense, a higher attendance might have been achieved with a chemotherapy-periodized exercise prescription. The majority of the BENEFIT patients received weekly chemotherapy at least for some part over the course of therapy. Based on individual feedback of patients, weekly chemotherapy appeared to hinder them to attend the two prescribed exercise sessions per week, because of the 24-hour prohibition to exercise after each admission, the strong side-effects in the days thereafter, as well as administrative reasons such as the conflict of medical appointments, family or work duties with the appointment schedule of the training facilities. This was partly also reported from patients in previous studies (Foucaut et al. 2019; Kirkham et al. 2020; van Waart et al. 2020). If a patient received different regimens, the weekly regimens mostly occurred rather after biweekly or three-weekly regimens. This might be one reason contributing to the decline of the group attendance per training week (i.e., over the course of chemotherapy). Besides the chemotherapy regimen, the duration of the chemotherapy may need to be taken into account. An association between a longer chemotherapy protocol and a lower attendance at exercise interventions could be observed in previous studies (Courneya et al. 2014a; Kirkham et al. 2018; Lund et al. 2019). About a third of patients exercised twice weekly at least within the first five weeks. The patients exercising the prescribed two exercise sessions a week did not remain the same, but rather changed throughout the intervention phase.

Most patients reported in the biweekly training calls that the chemotherapy-related side-effects, but also time issues related to either the appointment schedule of the training facilities, medical appointments, or family duties/events were the reasons for not being able to attend both weekly exercise sessions. This would be in line with the observations of a previous study (Foucaut et al. 2019) and the results of the multiple regression analyses. The investigation of an association between chemotherapy side-effects and the attendance at exercise interventions in the BENEFIT study revealed that patients with pain and/or nausea attended less exercise sessions than patients without these symptoms. However, these associations appeared to be statistically significant only for nausea. An association between pain and attendance at exercise interventions could be observed despite failing statistical significance (*ß* = 12.07; *p* = 0.12). This is in line with a previous study of Courneya and colleagues (2008), in which the authors asked the patients to provide a reason for each missed session (Courneya et al. 2008a). Nausea was the seventh most common barrier for missing an exercise session and accounted for 5% of all unattended exercise sessions (Courneya et al. 2008a). In their study, fatigue was the second and pain the eleventh most common barrier for not attending an exercise session (Courneya et al. 2008a). The association between attendance at exercise sessions and chemotherapy-related side-effects, mostly fatigue, is contradictory in the current literature, as some studies observed an association (Backman et al. 2016; Kirkham et al. 2020; Lavallée et al. 2019; Witlox et al. 2019) whereas others did not observe an effect of these side effects on attendance (Courneya et al. 2014a; Lund et al. 2019). The results of the multiple regression analyses did not reveal any statistically significant effects for pain and no influence of fatigue on the attendance at either exercise intervention. The comparisons need to be interpreted with caution, as the BENEFIT analyses are based on chemotherapy-related side-effects that were assessed during chemotherapy, whereas previous studies mostly investigated the influence of the chemotherapy-related side-effects on the attendance at exercise interventions before starting therapy (Bland et al. 2018; Courneya et al. 2014a; Daley et al. 2007a; Husebø et al. 2013; Lund et al. 2019; Stalsberg et al. 2022; Witlox et al. 2019) or after completing the cancer therapy (Bland et al. 2018; Courneya et al. 2014a; Courneya et al. 2008b). This may have left to over- or underestimation of the actual association as it may be assumed that the side-effects accumulate with the progression of the chemotherapy.

Another possible explanation for the lower attendance at the exercise interventions of the BENEFIT study compared to other exercise intervention studies may be the low PA behavior in the 12 months prior to study start. As defined in the exclusion criteria, patients, who already performed a systematic exercise training, were not included in the study. No previous study reported this, which might be reflected in the higher PA behavior of their patients compared to the BENEFIT patients (Bolam et al. 2019; Courneya et al. 2014a; Hornsby et al. 2014; Lund et al. 2019; van Waart et al. 2020). The association between the previous PA behavior and the exercise attendance is divergent, as some studies do (Courneya et al. 2008b; Foucaut et al. 2019; van Waart et al. 2020) and some do not (Lund et al. 2019; van Waart et al. 2020) observe a statistically significant (positive) association. However, this needs to be considered, because inactive patients are not used to regular activity and exercise and, therefore, need to change their routine in order to start exercise (Markes et al. 2006). Another explanation may be that sports-minded women may be more likely to attend the exercise sessions during chemotherapy despite the treatment-related side-effects.

A further possible reason for the relatively low attendance may be the Covid-19 pandemic that affected the training period of 46.7% of the patients through the fear of infection and the necessity (and partly also governmental regulation) of wearing a medical mask. This may have made the training more demanding and uncomfortable. The median attendance of the patients that exercised prior to the Covid-19 pandemic commencement was higher than the median attendance of the patients that exercised during or after the Covid-19-pandemic. Additionally, several training facilities had further limitations including limited time slots for training. In this regard, the Covid-19 pandemic may be seen as a selection bias, because patients who participated in the study besides the ongoing pandemic and the therewith related limitations, may be less anxious and/or more motivated.

Further, the training setting might have affected the attendance. The BENEFIT patients performed their training typically in public gyms, with oncological trained staff. Although likely together with other (healthy or ill) people at the training space in the gym, they usually exercised on their own. In contrast, one of the other studies including breast cancer patients under neoadjuvant chemotherapy performed personal training cycle sessions (Hornsby et al. 2014) and another study group-based resistance exercise with fifteen patients per group biweekly (Lund et al. 2019). It may be possible that a personal training may lead to a higher attendance due to the high attention the patients receive, whereas group sessions may increase the attendance through the social interaction with other patients. A pilot randomized controlled exercise intervention study compared a group dynamics-based (N=14; aerobic and resistance exercise with additional techniques to strengthen group cohesion) with an individual (N=12, same aerobic and resistance training as group dynamics-based exercise arm) exercise intervention in breast cancer patients (Leach et al. 2019a). The authors observed that the individual training group had a higher attendance compared to the group dynamics-based arm (Leach et al. 2019a).

In this regard, also the type and the patient’s perception of the training itself may play an important role. In the BENEFIT study, the AT was performed mostly on stationary bikes, which may have been perceived as rather boring and monotonous, as was occasionally reported by patients. The attendance differences between the randomization arms (AT versus RT) were statistically not significant ($p > 0.05$). But, irrespective of the randomization, the majority (84%) of the patients rated their exercise intervention as ‘good’ or ‘very good’, and those attended statistically significantly more exercise sessions compared to the patients who rated their intervention as ‘poor’, ‘very poor’ or ‘OK’. There was no statistically significant influence on the attendance by having received the preferred intervention (i.e. the intervention that a patient would have chosen prior to study start, if it would have been possible to choose).

The attendance at the exercise interventions of the BENEFIT study was observed to have a statistically significant negative association with BMI and educational level. Patients with a higher BMI attended statistically significantly less exercise sessions, which was also observed in previous studies (Courneya et al. 2014a; Foucaut et al. 2019; Lund et al. 2019; Witlox et al. 2019).

Patients with middle (i.e., high school degree) or academic education (i.e., diploma qualifying for university or university degree) attended more exercise sessions compared to the patients with an education below a high school degree. The educational background may be related to the understanding of the benefits of exercise. Patients with higher education might thus be more willing to undertake whatever is necessary to exercise, which may be related to the study participation, particularly during the Covid-19-pandemic. It may be also associated with the socioeconomic status. A lower socioeconomic status may be related to the necessity to work besides illnesses like cancer, even though the health care system in Germany pays for cancer-related sick-leave. The paid sick-leave is usually not the full salary, but a percentage of it, thus raising the necessity to work in order to avoid facing financial constraints. Having a full-time job may reduce the time available for exercising and, thus, reduce the attendance at exercise interventions. Unfortunately, the reasons due to which the 32.2% of the BENEFIT-patients kept working were not assessed. However, of those, who were still working, 28 patients (71.8%) had a middle or lower education. This may reveal an association between the education, the socioeconomic status, and a rather lower attendance to exercise interventions. Thus, a more targeted approach and offers to reach this population group are needed to enable the exercise participation. Socioeconomically deprived patients might benefit from financial help like the refund of the transportation cost needed to visit the training facility.

Further statistically significant associations were found with the marital status, with partnered or married patients having attended significantly more exercise sessions. The reason might be the support from the family and partner regarding everyday duties such as, e.g., care of the household and children, but also motivating and driving the patient to the training facility (van Waart et al. 2020). However, these observations need to be interpreted with caution as only 26 of the patients (21.7%) were not partnered. In contrast, no association could be observed between the attendance at the exercise intervention and the perceived social support, however, the majority of patients reported very high social support values (>90%).

Finally, the travel distance to the training facility could impede the attendance at exercise intervention as was observed in a previous study (Courneya et al. 2014a). In contrast, the multiple regression analyses in BENEFIT did not reveal any association of the travel distance with the attendance at the exercise sessions. However, this was not surprising, since patients were referred to training facilities as convenient and close to their homes as possible.

4.3 Training maintenance after end of exercise interventions

Besides attending the training during the exercise intervention, its sustainability is also of interest. Thus, the maintenance of the training after the end of the BENEFIT interventions was investigated. The patients either continued their training of the exercise intervention for a longer time (47.1%) or discontinued (52.9%) the training with completing the exercise intervention. Of the patients, who continued the training of the exercise intervention for some time beyond the intervention phase, 50% of the patients discontinued the training within 6 months post-intervention. The rest of the patients continued the training until the last study assessment. These results are in line with the systematic review and meta-analyses (Goldschmidt et al. 2022) and other previous studies, showing that the PA and PE behavior decreases 6 months post-intervention (An et al. 2020a; Bock et al. 2013; Schmidt 2017).

Patients in the RT group tended to maintain their exercise longer in comparison to AT and CG, but the difference was not statistically significant, which is in line with a previous study of Courneya and colleagues (2009) (Courneya et al. 2009). This may be related to the number of included eligible patients in these analyses, because more patients of the RT group had completed at least one follow-up assessment point compared to CG. Additionally, in contrast to RT (17.5%) and AT (15.4%), 60.0% of the patients in the CG had to be excluded from the analyses, because of their attendance to none or up to 6 exercise sessions.

Another possible reason for the statistically non-significant differences between RT, AT and CG with regard to the training maintenance, may be the training itself. More patients of AT reported in the biweekly training adherence calls that they perceived their training on one endurance machine, mostly a cycle ergometer, as boring and monotonous. In contrast, RT and CG had to change the machines regularly and, thus, may have been able to interact with others. However, no patient reported to skip any exercise sessions due to the training itself, i.e., because it was perceived as monotonous. This was also not reflected in the training evaluation with 88.1 % of the patients who had rated their training as ‘good’ and ‘very good’.

Possible reasons for training discontinuation have been investigated, but revealed mixed and to some extent opposing findings as some observed, e.g. post-interventional fatigue, depression and/or anxiety as a predictor of exercise maintenance (An et al. 2020a; Brunet et al. 2014; Courneya et al. 2009) and some did not (Schmidt et al. 2017). Yet, the patient's perspective was not yet sufficiently considered (Depenbusch et al. 2022; Eng et al. 2018).

The patients, who continued their training beyond the intervention phase reported their physical and mental well-being as the most important reasons for the training maintenance after exercise interventions. The benefits of PA and PE on the physical well-being and health were also identified as a possible determining factor to be physically active in a previous review (Browall et al. 2018). Despite the perceived benefit for their physical and mental well-being, 50% of the patients, who initially continued their training beyond completing the exercise intervention, discontinued their training after a median 6 months post-intervention. The most frequent reported reasons entailed a lack of time, the distance to the training facility and the Covid-19 pandemic. These reasons were also often reported by the patients who quit their training immediately after end of exercise intervention, yet, the most frequently reported reason was the change to a different sport. More specifically, of all patients who discontinued their training immediately or some time after end of the exercise intervention, 42.3% reported the change to different types of activities and exercises. Primarily reported were aerobic exercises that were done outside like (Nordic) walking or running, but also swimming and cycling, Yoga, fitness or gymnastics and also resistance training in form of functional or general strength training. Unfortunately, it was not assessed, if the patients performed this exercise with a frequency, intensity, and duration similar to their previous exercise prescriptions. However, these previously rather inactive patients apparently remained physically active to some extent after the BENEFIT intervention. Thereby, only one fourth of the patients discontinued the training of the exercise intervention without reporting to engage in any other kind of activity or exercise.

The barrier of a too long travel distance to the training facility is somewhat surprising, as during the study intervention all patients were placed in a training facility as close to their home as possible. Prior to study entry, the chosen training facility and the driving distance was discussed with each patient to ensure adherence at the exercise interventions. It may be possible that the patients did not perceive the travel distance restrictive during the intervention, which was often during sick leave, due to the amount of free time or the perceived importance of the study for their health. But, this may have changed to perceiving the travel distance as too burdensome after completing the cancer treatment, when likely returning to work or other day-to-day tasks, particularly because the travel distance was not observed to be associated with the attendance at the exercise interventions (Goldschmidt et al. 2024b).

Additionally, patients were only able to continue the training if they paid for the training out of their own pocket. The training-related costs did not only include the membership for the gym, but may have also entailed the transport to the gym irrespective of its type (car or public transport). It was observed that the availability of a car may promote (Browall et al. 2018), whereas the unavailability of health care reimbursed programs hinder PA and PE (Depenbusch et al. 2022). Similarly, in a large survey among 1,299 cancer survivors, the majority of patients (57.9%) reported the ‘lack of therapeutic programs that are reimbursed by health care insurances’ as a barrier to PA (Depenbusch et al. 2022).

However, depending on the distance to the training facility, not only the costs need to be considered, but the time that is needed to go to the gym, to exercise and to return home. A lack of time was the most reported reason in the patients that first continued their training for some time but then discontinued, and the second most frequent reported reason in the patients who immediately quit their training with the end of the intervention. There are multiple factors related to a lack of time, including the care of children and being currently employed. These factors were also observed in the review of Browall and colleagues (2018) (Browall et al. 2018). They noted that women may not take their time for PA due to their everyday demands, including taking care of the children or working (Browall et al. 2018). In contrast, in the BENEFIT study current employment and having children below the age of 18 years seemed to rather have encouraged the patients to maintain the training after end of intervention. More of the patients, who reported that they were still working despite their cancer diagnosis and chemotherapy, continued their training immediately after end of intervention and also maintained it for a longer time than the patients on sick leave. This observation is somewhat surprising, because being employed is usually associated with less free time. Since the health care system in Germany pays for about 18 months a sum of 70% of the previous gross salary for cancer-related sick-leave, cancer patients usually do not necessarily have to work. Thus, working beside the cancer treatment may be possibly related to having no or only mild side-effects, a stronger personality, to being better organized, or the necessity to work, because of self-employment. One could speculate that these patients' characteristics might be associated with a greater stamina to continue exercising.

Irrespective of the employment status, younger patients tended to maintain their exercise slightly longer than the older ones. Further, younger BENEFIT patients without underaged children more often discontinued the training immediately after the end of the intervention, compared to younger patients with underaged children, who tended to maintain the training for more than 30 months. This observation is somewhat surprising because it would suggest that younger patients with underaged children may have less time for exercise, but probably children may be seen as a reason to stay healthy and fit (Browall et al. 2018). Unfortunately, the role of the perceived and actual support through the family or partner with regard to the take-over of the duties related to household and children could not be investigated. However, the married patients of the BENEFIT study maintained their training significantly longer, whereas not married patients quit the exercise immediately or soon after the intervention. The unequal balance of patients per group need to be considered with 52 partnered and only 11 unpartnered patients (N=6), widowed (N=1) and single (N=4). Nevertheless, the social support from the family, particularly the partner should be taken into consideration - as was already suggested for the analyses on attendance. A significant positive association between social support and the PA level has been frequently observed (Trost et al. 2002), thus, addressing the patient's supportive needs may improve the uptake and maintenance of training. The support as a necessary requirement for the engagement in PA and exercise needs to be further elaborated.

In contrast with previous studies (Courneya et al. 2009; Schmidt et al. 2017), it could be observed that patients with lower to middle education tended to maintain their exercise intervention as long as higher educated patients. However, the number of patients, who maintained the training beyond the exercise intervention was higher in the patients with academic education, i.e., more academic patients maintained their training compared to patients with a high school degree or lower. The difference in the number of patients continuing the training beyond the exercise intervention phase may be related to a more extended knowledge about the benefits of exercise throughout life irrespective of any disease. An association between education and the PA and PE behavior could be observed (Steindorf et al. 2020; Trost et al. 2002). Furthermore, the education may be linked to the socioeconomical status, which itself was observed to be associated with the PA and PE behavior too (Steindorf et al. 2020; Trost et al. 2002). A lower education is linked with a lower socioeconomical status due to which the patients may face financial constraints that do not allow to continue the training in the training facility on their own expense.

The attendance at the exercise interventions was related to the training maintenance. This may be due to similar influencing, rather supporting determinants like the marital status that may represent the social support and the academic education, which may depict a better understanding of the benefits of PA within the cancer continuum and beyond. However, the continuation of the training after completing the intervention phase requires further amendments of the patients including the financial stability to be able to pay for the training and related costs. Furthermore, patients usually go back to their everyday life, including their duties of work, household and children after completing their therapy denoting the need to integrate their training in a busy schedule.

4.4 Long-term effects of the exercise interventions of the BENEFIT study

In line with the systematic review and meta-analysis, the analyses of the BENEFIT study revealed that the patients maintained their training of the exercise intervention for up to 60 months post-intervention, with a median continuation time of 19.0 months (Q1, Q3: 5.5, 36.0) (Goldschmidt et al. 2024a; Goldschmidt et al. 2022). Overall, 43 patients discontinued the training immediately or within 6 months after completing the exercise intervention and did not report to engage in any other kind of PA or PE. This is in line with the results of the systematic review and meta-analysis, in which a moderate intervention effect on MVPA at 6 months post-intervention could be observed that thereafter decreased.

Only 25% of all patients reported not to engage in any activity or exercise after discontinuing the exercise intervention. This is a very promising result, when considering that the BENEFIT patients had to be rather physically inactive in order to be included in the study. Thus, the exercise interventions during or after neoadjuvant chemotherapy seem to have a sustainable influence on the medium- and longer-term PE behavior between 6 months up to 60 months after completing the exercise intervention. Thereby, more patients who attended between 50%-75% of their prescribed exercise sessions maintained their training of the exercise intervention longer compared to patients with a higher or lower attendance. This may lead to the assumption that patients need to attend a certain amount of exercise sessions in order to change their PA behavior, as was suggested in a previous review (Markes et al. 2006). The suggested underlying interaction may be drawn back to shared influencing factors between the attendance at exercise sessions and the training maintenance after end of intervention. The following variables appeared to have a positive influence on the attendance at exercise intervention as well as the training maintenance: Being partnered, academic education, good or better rating of the exercise training.

It may be assumed that the marital status may be related to the amount of social support, i.e., partnered patients may receive more social and/or practical support than patients without a partner. This may include but is not limited to the takeover of more or all activities of daily living like taking care of the household and children, but also regarding the perceived support. The support may not only act as a motivator for a more physically active lifestyle, but further enable the patients to take their time for exercise, which may be not the case in single (parent) patients.

The underlying assumption of academic education is a broader knowledge about the benefits of PA and PE on physiological and psychological health within the cancer continuum and beyond. An association with both, attendance at exercise interventions as well as training maintenance could be observed. The reason of the influence of academic education may not only be the knowledge, but also the socioeconomic status that was observed to be related with lower education - as was already indicated for the analyses on attendance. Previous studies observed an association between education as well as the socioeconomical status and the PA behavior (Steindorf et al. 2020; Trost et al. 2002).

A rather positive rating of the exercise intervention appeared to enhance the attendance at exercise interventions and training maintenance. This appears to be intuitively, as patients who do not enjoy the training, won’t regularly attend nor continue it.

Divergent influencing factors could be observed for attendance at exercise interventions and training maintenance with regard to age, children < 18 years of age and the employment status. The analyses revealed no associations between these three variables and the attendance at exercise interventions. In contrast, younger patients, younger patients with underaged children and patients that worked at baseline tended to maintain their training longer than their respective counterparts, i.e., older patients, younger patients without underaged children or patients on sick-leave. The different influence of these variables on exercise attendance and training maintenance, besides the low number of patients in the analyses of influencing factors on training maintenance, may be the overall life-setting or the personal characteristics or perceptions of the patient. Therefore, it appears to be important to directly ask the patients for reasons to (dis)continue the training after end of intervention. In the present analyses no obvious associations between the influencing variables and the reported reasons were observed nor specifically investigated. However, it appears to be that, for example, a lack of time and the long travel distance to the training facility, may reflect time or financial constraints that may be related with the current employment status and therewith, less time to exercise when the patients returned to their previous lives. However, this needs to be further investigated in future studies. It needs to be considered that the participation at an exercise intervention study, particularly during doubtful times like it is during cancer continuum, may reflect particular circumstances related to higher motivation and commitment to the study protocol. That may change after completing the exercise intervention, where the patients need to transition from an organized exercise intervention to a feasible and affordable training that is integrated in their daily life on their own.

4.5 Strengths and Limitations

The present thesis addressed some gaps in the current literature regarding attendance at exercise interventions and training maintenance and, thus, contributes to the overall knowledge in this field. However, some limitations need to be addressed.

First, the meta-analyses only included a small number of studies within the subgroups, which hindered meaningful comparisons and investigations of possible associations between the type, intensity, setting (e.g., group-based versus individually, supervised versus unsupervised), frequency and timing (e.g. during versus after cancer treatment) of the exercise intervention and the training maintenance after exercise interventions. Furthermore, the identified publications reported only insufficiently about the attendance at exercise interventions and the training maintenance of the respective exercise interventions in the long-run. Alike insufficiently investigated and reported was the PA and PE behavior of the control groups. Contamination of the control groups may have contributed to the mixed findings regarding intervention effects on the long-term PA behavior. Further, there is no gold standard for assessing PA and PE, thus different assessment methods have been used. For each of these assessment types, different benefits and limitations need to be considered. For accelerometers this includes the inability to assess every type of exercise and its intensity correctly. The self-reported PA and exercise behavior is prone to over- or underreporting dependent, e.g., on the social desirability. Further, exercise intervention studies are prone to selection bias, because usually only patients who are already interested in PA and know the importance and benefits of PA and/or already engage in regular PA participate in exercise intervention trials (Foucaut et al. 2019).

According to the inclusion and exclusion criteria of the BENEFIT study, selection bias needs to be considered, because only less physically active or inactive patients were included. Additionally, in line with Foucaut and colleagues (2019), it may be assumed that only patients, who already have a better understanding of the benefits of exercise during cancer treatment and/or are more interested in exercise are willing to participate (Foucaut et al. 2019). Therein, the placement of the patients in training facilities as close to their homes as possible solely and with regard to the Covid-19 pandemic have also resulted in a selection bias. The placement in a training facility was discussed with each patient prior to study entry, but it may have been the case that in a few cases it was not possible to find a close training facility, which the patient could be easily reached (e.g., without a car, due to time or financial constraints). These patients did then not participate in the study. During the Covid-19 pandemic and the related lockdown, the training was only possible in certain training facilities that may have required the patient to drive longer, which was only taken upon by a few patients. This may be not only related to the motivation, but rather the socioeconomical status and the related ability to do so.

The variables that were investigated as possible influencing factors of the attendance at exercise interventions and the training maintenance after exercise interventions were assessed at baseline or mid-intervention and were not assessed at any further follow-up study measurement, even though they could have changed and, thus, may have changed the here observed results. Other potentially important influencing factors like self-efficacy, perceptions of a patient regarding exercise, or characteristics of the patient’s personality were not assessed in the BENEFIT study, but may have an influence on both the attendance at exercise intervention and the training maintenance. This should be investigated in future studies.

The investigation of self-reported questionnaires inherits the risk of socially desirable, mostly overreporting. Further limitations that need to be considered were the retrospective assessment of the training preferences, which may have resulted in a recall bias and may also have been influenced by the experienced side-effects, as was reported from few patients.

The analyses regarding training maintenance in only N=68 participants had a lack of statistical power. Thus, there was an increased risk for a type II error. Additionally, the assessment of maintenance was not very precise as it was not specified, which training needed to be performed with regard to frequency, intensity, time and type of exercises to be accounted as similar to the received exercise intervention and, therefore, as being considered 'maintaining the training' of the exercise intervention.

Assessing the attendance instead of the adherence to either exercise intervention may be regarded as another limitation. It may be assumed that every kind of activity is beneficial for this sedentary population, but future studies should consider the attendance, as well as adherence rate with the related reasons for non-attendance and reduction of the prescribed exercise program.

The assessment of the attendance at the exercise sessions with CRFs together with the list of signatures is considered a strength of the study, as this may have reduced the risk of overreporting. Further strengths include the pre-specified follow-up assessments of the BENEFIT study, because it enables the investigation of the training maintenance and also the impact of exercise interventions on the PRO in the longer run. The randomization into AT and RT during or after neoadjuvant chemotherapy enables the comparison and investigation of the impact of two different exercise interventions (AT/RT) at two different points in time (during or after NACT) and its influence on the exercise attendance and training maintenance. It also reveals insights how future exercise interventions may be conducted for more sustainable effects on the patient’s health.

4.6 Implications and Conclusions

The presented analyses of the effects of exercise interventions on PA and PE as well as its determining factors in breast cancer patients contribute to the existing knowledge in this field by investigating the influence of pure exercise interventions without any additional behavior change, social or cognitive component, by considering more defined and longer follow-up periods, and by comparing different types of PA.

The systematic review of the current literature and meta-analyses, which found significant effects of pure exercise interventions on short- and longer-term PA behavior of small to moderate effect sizes, suggest that some but not all cancer survivors who received an exercise intervention have increased PA levels for up to 60 months beyond completing an intervention. The only small to moderate effect sizes as well as the observed decline of the effect over time, however, indicate a high potential for further improvements regarding the sustainability of exercise interventions. An intervention providing only exercise may not be enough for all cancer patients to stay active long-term. The training maintenance after an exercise intervention may be improved by adding behavioral, social, and cognitive elements.

The analyses of the BENEFIT study showed that the training of the intervention was continued by the cancer patients on their own responsibility and at their own expense for a median of 19 months after end of intervention. Only a quarter of patients discontinued exercising, and hence, likely returned to their pre-diagnosis physical (in)activity. Thus, the BENEFIT exercise interventions might have contributed to the uptake and maintenance of exercise in three-quarters of previously rather inactive breast cancer patients. Since patient-reported reasons for training discontinuation included a lack of time, the long travel distance and the costs related to the training, and patients who were older, less educated, or unpartnered more often discontinued the training, the number of patients maintaining their training as well as the duration of training maintenance may be increased with financial, practical and social support.

Furthermore, the analyses of the training maintenance after the end of the BENEFIT interventions revealed no statistically significant superiority of either aerobic or resistance exercise on the training maintenance. However, to draw clear conclusions regarding which type, timing and overall setting of exercise interventions may be most effective to improve training maintenance and PA behavior in the long run, more studies with more and longer follow-up, different exercise regimens (group-based vs. individual training, aerobic vs. resistance vs. combined training) at different intensities and points in time (during versus after therapy) are needed.

The attendance at the BENEFIT exercise interventions was on average low and decreased over the course of the chemotherapy, even though the patients could have adjusted their exercise intensity according to their needs. But while some patients never started exercising, others exercised almost consistently twice a week. The attendance at the scheduled sessions may be important for an exercise intervention to be effective with regard to clinical endpoints but also with regard to the longer-term PE and PA behavior. Besides education and familial status, attendance seemed impacted by high BMI and the presence of nausea or pain. These potential barriers for training attendance should be addressed by providing appropriate support and adjusting the training as needed. The study further showed that patients who are less educated or live alone may need more support to participate in more exercise sessions.

In conclusion, the BENEFIT exercise interventions tended to be successful in the uptake and maintenance of exercise in previously rather inactive breast cancer patients, of which approximately three quarters remained physically active until ≥24 months after surgery (i.e., the last study assessment). The results reveal the need for more tailored approaches to increase exercise maintenance and the long-term PA behavior of breast cancer patients for more than 12 months after completing an exercise intervention, which may include social, practical, and financial help or live-remote exercise offers.

5 Summary

Despite the well-known safety and beneficial effects of physical activity and exercise on the well-being during and after cancer treatment, breast cancer patients commonly decrease their physical activity after the cancer diagnosis and usually remain at a low activity level throughout the treatment. Exercise interventions can prevent physical inactivity during the intervention. However, data regarding the longer-term physical activity and exercise behavior of breast cancer survivors after completing an exercise intervention is still limited. To sustainably increase the physical activity behavior well beyond the intervention phase, it is relevant to know the influencing factors. Thus, the aim of this dissertation was to investigate patterns and determinants of attendance at exercise interventions during chemotherapy and of training maintenance after the end of the interventions, considering the patients' perspective on reasons to (dis)continue exercising. The present thesis investigated these questions in the BENEFIT study, an ongoing 3-arm randomized controlled exercise intervention study in breast cancer patients undergoing neoadjuvant chemotherapy, who were either allocated to an aerobic or resistance training during the chemotherapy or a resistance training after their breast surgery. Additionally, the current evidence regarding the impact of exercise interventions on the short- and long-term physical activity behavior in breast cancer patients at different treatment stages had been investigated by conducting a systematic review and meta-analyses. The systematic review identified 27 RCTs with 4120 participants, of which 11 RCTs with 1545 participants had appropriate data for the meta-analyses. It depicted that exercise interventions may increase the physical activity behavior of breast cancer patients in the longer-run, showing small to moderate effects up to 5 years post-intervention for total physical activity and up to 20 months for moderate-to-vigorous physical activity. However, the effects decreased over time and appeared to be statistically significant for moderate-to-vigorous physical activity 6 months post-intervention only.

The analyses of attendance included all 122 BENEFIT patients randomized to training during neoadjuvant chemotherapy (equally balanced in both groups). The data showed a decrease

in attendance at the training sessions over the course of chemotherapy with an average individual attendance at 44.1% of scheduled sessions, without significant difference between aerobic and resistance training. Lower exercise attendance was associated with a higher BMI, lower education, being unpartnered, having nausea, having pain and higher level of walking in the 12 months prior to study entry.

Training maintenance was analyzed with questionnaires set-up for this dissertation and completed by 68 patients (aerobic exercise: 25, resistance exercise: 29, control group: 14). They assessed the patients' personal reasons to (dis)continue the training after completing the exercise intervention and provided an insight into the sustainability of exercise interventions. In line with the meta-analyses, the patients mostly discontinued the exercise training immediately or within 6 months after completing the exercise intervention, whereas some maintain the training for up to 60 months post-intervention. Among those who maintained the training the median continuation time was 19.0 months (Q1: 5.5 months, Q3: 36.0 months). The main reasons for training continuation were physical and psychological well-being, whereas the most frequently reported reason for training discontinuation was the change to a different exercise, followed by a lack of time and the long travel distance to the gym. The majority of patients remained active, either through maintaining their training of the exercise intervention or for those, who did not maintain their training, by changing to different exercises (52.8%). For those, who did not continue exercising nor changed to different exercise (25%), social, practical, and financial support may have enabled to establish a feasible and affordable training in their daily life after completing the exercise intervention.

The BENEFIT exercise interventions successfully contributed to the uptake and maintenance of exercise in previously rather inactive breast cancer patients. Furthermore, the analyses revealed an important insight into the patient's reasons to (dis)continue the training beyond the exercise intervention phase that enables adjustments in future studies to improve the sustainability of exercise interventions and, therewith, the physical and psychological well-being in breast cancer patients during and after cancer treatment.

6 Zusammenfassung

Unabhängig der gut belegten Sicherheit als auch der positiven Effekte von körperlicher Aktivität und Sport während und nach einer Krebsbehandlung, reduzieren die meisten Brustkrebspatientinnen ihre körperliche Aktivität häufig mit Erhalt der Diagnose und bleiben über den Zeitraum der Therapie hinweg nur wenig aktiv. Sportinterventionen können körperlicher Inaktivität über den Zeitraum der Intervention vorbeugen. Allerdings ist die Datenlage in Bezug auf das langfristige körperliche Aktivitätsverhalten nach Abschluss einer Sportintervention noch nicht eindeutig. Um das körperliche Aktivitätsverhalten nachhaltig steigern zu können, ist es nötig, mögliche Einflussfaktoren zu kennen. Daher war das Ziel der vorliegenden Arbeit, den Verlauf und die Einflussfaktoren der Teilnahme an Sportinterventionen über den Zeitraum der Chemotherapie und der Trainingsfortführung nach Abschluss der Intervention unter Berücksichtigung der patientenbezogenen Gründe zur (Nicht-) Fortführung des Trainings, zu untersuchen. Die vorliegende Arbeit untersuchte diese Fragen im Rahmen der BENEFIT-Studie, einer 3-armig randomisiert kontrollierten Sportinterventionsstudie in Brustkrebspatientinnen unter neoadjuvanter Chemotherapie, die entweder einem Ausdauer- oder einem Krafttraining über den Zeitraum der Chemotherapie, oder einem Krafttraining nach der Burstoperation zugelost wurden. Zusätzlich wurde im Rahmen einer systematischen Übersichtsarbeit und Meta-Analysen die aktuelle Evidenz hinsichtlich der Auswirkungen von Sportinterventionsstudien auf das körperliche Aktivitätsverhalten von Brustkrebspatientinnen in unterschiedlichen Therapiestadien untersucht.

Insgesamt konnten 27 randomisiert kontrollierte Studien mit 4120 Teilnehmerinnen für das systematische Review identifiziert werden, von denen 11 randomisiert kontrollierte Studien mit 1545 Teilnehmern geeignete Daten für die Durchführung einer Meta-Analyse hatten. Die Analysen ergaben, dass Sportinterventionen das körperliche Aktivitätsverhalten von Brustkrebspatientinnen längerfristig steigern können, bei denen sich kleine bis moderate Effekte bis zu 5 Jahre nach der Intervention für die gesamte und bis zu 20 Monate für die moderate bis anstrengende körperliche Aktivität zeigten. Allerdings nahmen diese Effekte über die Zeit hinweg ab und fielen ausschließlich 6 Monate nach Abschluss der Sportintervention für die moderate bis anstrengende körperliche Aktivität statistisch signifikant aus.

Die Trainingsteilnahme von allen 122 BENEFIT- Patientinnen, die in ein Training über den Zeitraum der neoadjuvanten Chemotherapie randomisiert wurden (gleichmäßig auf beide Gruppen verteilt) wurde analysiert. Die Trainingsteilnahme nahm über die Chemotherapie hinweg ab mit einer mittleren individuellen Trainingsteilnahme von 44,1%, die sich statistisch nicht signifikant zwischen der Ausdauer- und der Krafttrainingsgruppe unterschied. Eine geringere Trainingsteilnahme wurde bei Patientinnen mit einem höheren BMI, geringeren Bildungsniveau, alleinstehenden Patientinnen, Patientinnen die unter Übelkeit litten, Schmerzen hatten und Patientinnen, die in den letzten 12 Monaten vor Beginn der Studie mehr spazieren gegangen sind, beobachtet.

Die Trainingsfortführung wurde zusätzlich mit, für die Dissertation eignes erstellten Fragebögen analysiert, die von 68 Patientinnen (Ausdauertraining: 25, Krafttraining: 29, Kontrollgruppe: 14) ausgefüllt wurde. Mit diesen wurden die persönlichen patientenbezogenen Gründe zur (Nicht-) Fortführung des Trainings nach Abschluss einer Sportintervention erfasst und gaben einen Einblick in die Nachhaltigkeit von Sportinterventionen. In Übereinstimmung mit den Beobachtungen aus der Meta-Analyse, beendeten die meisten Patientinnen ihr Training direkt oder innerhalb von 6 Monaten nach Abschluss der Sportintervention, während manche Patientinnen, ihr Training bis zu 60 Monate nach Abschluss der Sportintervention weiterführten. Diejenigen, die ihr Training weiterführten, führten es im Median für 19 Monate weiter (Q1: 5,5 Monate, Q3: 36,0 Monate). Die Hauptgründe zur Fortführung des Trainings stellten das physische und psychische Wohlbefinden dar. Dem entgegen stellten die Hauptgründe zur Nichtfortführung der Wechsel zu einer anderen Sportart dar, gefolgt von einem Mangel an Zeit und die lange Anfahrt zum Trainingszentrum. Die Mehrheit der Patientinnen blieb entweder durch die Fortführung ihres Trainings oder bei Nichtfortführung des Trainings, durch den Wechsel in andere Sportarten aktiv (52.8%). Diejenigen, die weder das Training fortführten noch zu einer anderen Sportarten wechselten (25%), könnten von sozialer, praktischer und finanzieller Unterstützung profitieren, um ein machbares und erschwingliches Training in ihren Alltag zu integrieren.

Die BENEFIT-Sportinterventionen trugen erfolgreich zu der Aufnahme und Fortführung von Sport und Bewegung bei zuvor eher inaktiven Brustkrebspatientinnen bei. Darüber hinaus ermöglichten die Analysen einen wichtigen Einblick in die Gründe der Patientinnen ihr Training nach Abschluss der Sportintervention (nicht) fortzuführen. Dies ermöglicht es Anpassungen in zukünftigen Studien vorzunehmen, um die Nachhaltigkeit von Sportinterventionen und damit auch das physische und psychische Wohlbefinden von Brustkrebspatientinnen während und nach der Krebsbehandlung zu verbessern.

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8 Annex

8.1 Systematic review and meta-analyses

8.1.1 Search strategies of the systematic review and meta-analyses according to the PRISMA guidelines

Table 15: Search strategies in the database PubMed (Goldschmidt et al. 2022)

	"Category"	PubMed	Count at 31.01.2022
1	**Sustainability**	**maintain*[Tiab] OR maintenance [Tiab] OR sustain*[Tiab] OR upkeep [Tiab] OR uphold [Tiab] OR continue [Tiab] OR long-term [Tiab] OR longterm [Tiab]**	2,250,199
2	Exercise intervention	((Exercise OR "exercise"[Tiab] OR physical activity [Tiab] OR sport*[Tiab] OR fitness[tiab]) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomly[tiab]) OR (intervention [Tiab] OR training*[Tiab] OR program [Tiab]))) OR (aerobic exercise*[Tiab] OR endurance exercise*[Tiab] OR resistance exercise*[Tiab] OR strength exercise*[Tiab]) OR (aerobic training*[Tiab] OR endurance training*[Tiab] OR resistance training*[Tiab] OR strength training*[Tiab])	196,057
3	Population	"breast"[Tiab] OR "breasts"[Tiab] OR "mamma"[Tiab] OR "mammae"[Tiab] OR "mammas"[Tiab] OR "mammary"[Tiab]	529,485
4	Population	cancer*[tiab] OR neoplas*[tiab] OR tumor *[tiab] OR tumor *[tiab] OR carcinoma*[tiab] OR malignan*[tiab]	3,687,348
5	Population	(**Animals NOT Humans)**	4,958,947
6	Population	(Breast neoplasms OR ((breast OR (breast diseases) AND neoplasms)) AND humans)	321,108
7	Population	(#3 AND #4 NOT #5) OR #6	451,100
8	TOTAL	#7 AND #1 AND #2	617

Table 16: Search strategies in the database COCHRANE (Goldschmidt et al. 2022)

	"Category"	Cochrane - Trials	Count at 31.01.2022
1	**Sustainability**	**maintain* OR maintenance OR sustain* OR upkeep OR uphold OR continue OR long-term OR longterm**	336,773
2	Exercise intervention	((Exercise OR "exercise" OR physical activity OR sport* OR fitness) AND ((randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR randomly) OR (intervention OR training* OR program))) OR (aerobic exercise* OR endurance exercise* OR resistance exercise* OR strength exercise*) OR (aerobic training* OR endurance training* OR resistance training* OR strength training*)	157,344
3	Population	"breast" OR "breasts" OR "mamma" OR "mammae" OR "mammas" OR "mammary"	53,189
4	Population	cancer* OR neoplas* OR tumor * OR tumor * OR carcinoma* OR malignan*	235,961
5	Population	**Animals NOT Humans**	4,341
6	Population	(Breast neoplasms OR ((breast OR (breast diseases) AND neoplasms)) AND humans)	52,325
7	Population	(#3 AND #4 NOT #5) OR #6	52,447
8	TOTAL	#7 AND #1 AND #2	1,177

Table 17: Search strategies in the database Web of Science (Goldschmidt et al. 2022)

	"Category"	Web of Science	Count at 31.01.2022
1	**Sustainability**	**maintain* OR maintenance OR sustain* OR upkeep OR uphold OR continue OR long-term OR longterm**	3,572,023
2	Exercise intervention	((Exercise OR "exercise" OR physical activity OR sport* OR fitness) AND ((randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR randomly) OR (intervention OR training* OR program))) OR (aerobic exercise* OR endurance exercise* OR resistance exercise* OR strength exercise*) OR (aerobic training* OR endurance training* OR resistance training* OR strength training*)	620,197
3	Population	"breast" OR "breasts" OR "mamma" OR "mammae" OR "mammas" OR "mammary"	796,027
4	Population	cancer* OR neoplas* OR tumor * OR tumor * OR carcinoma* OR malignan*	4,744,442
5	Population	**Animals NOT Humans**	903,503
6	Population	(Breast neoplasms OR ((breast OR (breast diseases) AND neoplasms)) AND humans)	172,980
7	Population	(3 AND 4 NOT 5) OR 6	673,551
8	TOTAL	#7 AND #1 AND #2	2,165

Table 18: Search strategies in the database EMBASE (Goldschmidt et al. 2022)

	"Category"	EMBASE	Count at 13.07.2021
1	**Sustainability**	**maintain* OR maintenance OR sustain* OR upkeep OR uphold OR continue OR long-term OR longterm**	3080594
2	Exercise intervention	((Exercise OR "exercise" OR physical activity OR sport* OR fitness) AND ((randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR randomly) OR (intervention OR training* OR program))) OR (aerobic exercise* OR endurance exercise* OR resistance exercise* OR strength exercise*) OR (aerobic training* OR endurance training* OR resistance training* OR strength training*)	360794
3	Population	"breast" OR "breasts" OR "mamma" OR "mammae" OR "mammas" OR "mammary"	903189
4	Population	cancer* OR neoplas* OR tumor * OR tumor * OR carcinoma* OR malignan*	6511123
5	Population	**Animals NOT Humans**	827052
6	Population	(Breast neoplasms OR ((breast OR (breast diseases) AND neoplasms)) AND humans)	232
7	Population	(#3 AND #4 NOT #5) OR #6	719751
8	TOTAL	#7 AND #1 AND #2	1246

8.1.2 Systematic review and meta-analyses – Physical activity assessment methods

Table 19: Assessment method of the variable physical activity of all studies included in the meta-analyses (Goldschmidt et al. 2022)

Study	PA outcome(s)	PA measured with	Months after intervention
Bolam 2019 (Sweden) **(Bolam et al. 2019)**	MVPA (min/wk)	Accelerometry	20
Carayol 2019 (France) **(Carayol et al. 2019)**	MVPA (MET*min/wk)	GPAQ	6, 12
Cornette 2015 (France) **(Cornette et al. 2016)**	MVPA (MET*min/wk)	IPAQ	6.2
McNeil 2019 (Canada) **(McNeil et al. 2019)**	Total PA (min/day) MVPA (min/wk)	Accelerometry Accelerometry	3
Mutrie 2012 (Scotland) **(Mutrie et al. 2012)**	Total PA (min/week)	SPAQ	6, 18, 60
Rogers 2009 (United States) **(Rogers et al. 2009)**	Total PA (Daily PA counts) MVPA (min/wk)	Accelerometry Accelerometry	3
Rogers 2015 (United States) **(Rogers et al. 2015)**	MVPA (min/wk)	Accelerometry	3
Schmidt et al. 2017 (Germany) **(Schmidt 2017)**	Total PA (MET*min/wk) log-transformed	Walking, cycling, exercise adopted from SQUASH	3, 12
Steindorf 2014 (Germany) **(Steindorf et al. 2014)**	Total PA (MET*min/wk) log-transformed	Walking, cycling, exercise adopted from SQUASH	2, 6, 12
vanWaart 2015 (Netherlands) **(van Waart et al. 2015)**	Total PA (min/wk)	PASE	6
Witlox 2018 (Netherlands)(Witlox et al. 2018)	Total PA (min/wk)	SQUASH	4.5, 43.5

Only volitional or leisure PA was included in the table. GPAQ - global physical activity questionnaire, IPAQ - International physical activity questionnaire MET – metabolic equivalent of task, MVPA – moderate-to-vigorous physical activity, PA – Physical activity, PASE - Physical Activity Scale for the elderly, SPAQ – Scottish Physical activity questionnaire, SQUASH- Short Questionnaire to Assess Health-enhancing physical activity, wk - week

8.1.3 Risk of bias assessment

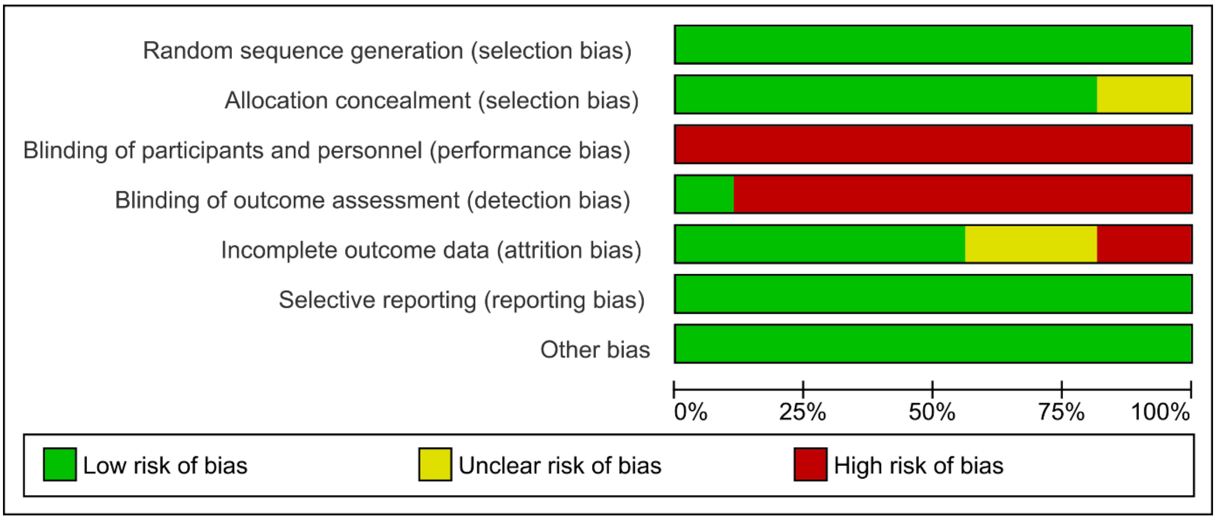
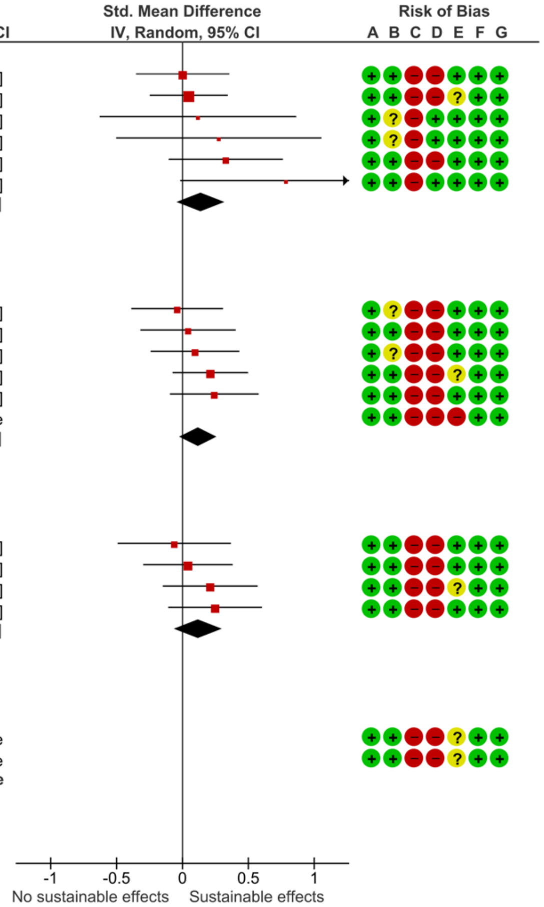


Figure 25: Risk of bias graph (Goldschmidt et al. 2022)

Figure 26: Risk of bias summary (Goldschmidt et al. 2022)

8.1.4 Forest plots for the total physical activity behavior – stratified according the investigated subgroups

Study or Subgroup	Mode *	Timing **	PA ***	Control Total	Experimental Total	Weight	Std. Mean Difference IV, Random, 95% CI
Total PA_Follow-up about 3 months							
Steindorf 2014	s	d	sub	57	57	26.9%	0.00 [-0.35, 0.35]
Witlox 2018	s	d	sub	77	87	38.6%	0.05 [-0.24, 0.34]
McNeil 2019_Low_PA	ns	a	obj	12	14	6.0%	0.12 [-0.62, 0.86]
McNeil 2019_HI_PA	ns	a	obj	12	12	5.5%	0.28 [-0.50, 1.05]
Schmidt 2017	s	d	sub	35	43	17.9%	0.33 [-0.10, 0.76]
Rogers 2009	ns	a	obj	11	14	5.2%	0.79 [-0.01, 1.58]
Subtotal (95% CI)				**204**	**227**	**100.0%**	**0.14 [-0.04, 0.32]**
Heterogeneity: Tau² = 0.00; Chi² = 4.37, df = 5 (P = 0.50); I² = 0%							
Test for overall effect: Z = 1.52 (P = 0.13)							
Total PA_Follow-up about 6 months							
vanWaart 2015_Onco-Move	ns	d	sub	59	59	18.0%	-0.04 [-0.38, 0.30]
Steindorf 2014	s	d	sub	54	55	16.6%	0.04 [-0.31, 0.40]
vanWaart 2015_OnTrack	s	d	sub	59	68	19.3%	0.10 [-0.24, 0.43]
Mutrie 2012	s	d	sub	95	82	26.8%	0.21 [-0.07, 0.49]
Carayol 2019	s	d	sub	59	69	19.3%	0.24 [-0.09, 0.57]
Cornette 2015	ns	d	sub	9	10		Not estimable
Subtotal (95% CI)				**326**	**333**	**100.0%**	**0.12 [-0.02, 0.27]**
Heterogeneity: Tau² = 0.00; Chi² = 1.96, df = 4 (P = 0.74); I² = 0%							
Test for overall effect: Z = 1.63 (P = 0.10)							
Total PA_Follow-up 12-20 months							
Schmidt 2017	s	d	sub	35	43	18.1%	-0.06 [-0.49, 0.36]
Carayol 2019	s	d	sub	57	68	29.2%	0.04 [-0.29, 0.38]
Mutrie 2012	s	d	sub	55	56	26.0%	0.21 [-0.14, 0.57]
Steindorf 2014	s	d	sub	57	57	26.6%	0.25 [-0.10, 0.60]
Subtotal (95% CI)				**204**	**224**	**100.0%**	**0.12 [-0.06, 0.30]**
Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 3 (P = 0.64); I² = 0%							
Test for overall effect: Z = 1.32 (P = 0.19)							
Total PA_Follow-up 43.5-60 months							
Witlox 2018	s	d	sub	51	59		Not estimable
Mutrie 2012	s	d	sub	41	43		Not estimable
Subtotal (95% CI)				**0**	**0**		**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



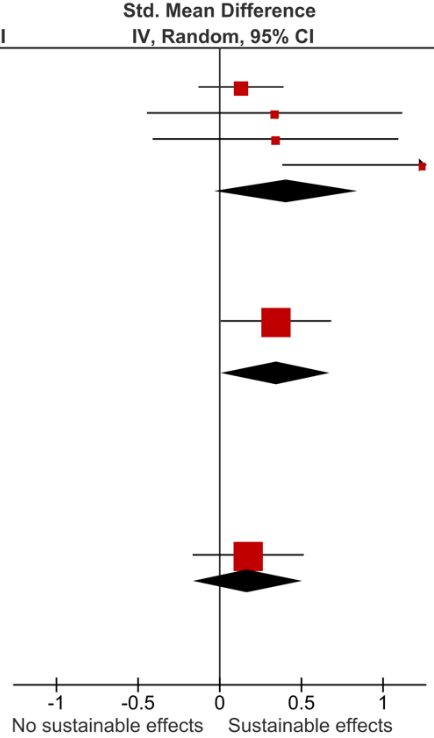
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

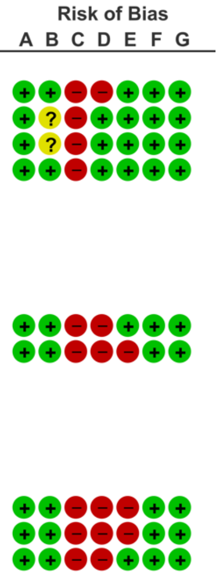
* Intervention mode s: supervised; ns: not supervised
** Intervention timing d: during cancer therapy; a: after cancer therapy
*** Assessment of physical activity obj: objective; sub: subjective

Figure 27: Forest plots of the sensitivity analysis for the outcome variable total physical activity (Goldschmidt et al. 2022)

8.1.5 Forest plots for the moderate-to-vigorous physical activity behavior – stratified according the investigated subgroups

Study or Subgroup	Mode *	Timing **	PA ***	Control Total	Experimental Total	Weight	Std. Mean Difference IV, Random, 95% CI
moderate and higher PA_Follow-up 3 months							
Rogers 2015	ns	a	obj	108	105	42.7%	0.13 [-0.13, 0.39]
McNeil 2019_HI_PA	ns	a	obj	12	12	19.5%	0.34 [-0.44, 1.11]
McNeil 2019_Low_PA	ns	a	obj	12	14	20.4%	0.34 [-0.41, 1.09]
Rogers 2009	ns	a	obj	11	14	17.3%	1.24 [0.39, 2.09]
Subtotal (95% CI)				**143**	**145**	**100.0%**	**0.41 [-0.03, 0.85]**
Heterogeneity: Tau² = 0.10; Chi² = 6.13, df = 3 (P = 0.11); I² = 51%							
Test for overall effect: Z = 1.81 (P = 0.07)							
moderate and higher PA_Follow-up about 6 months							
Carayol 2019	s	d	sub	59	69	100.0%	0.34 [0.01, 0.68]
Cornette 2015	ns	d	sub	8	9		Not estimable
Subtotal (95% CI)				**59**	**69**	**100.0%**	**0.34 [0.01, 0.68]**
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.02 (P = 0.04)							
moderate and higher PA_Follow-up 12-20 months							
Bolam 2019_RT	s	d	obj	48	58		Not estimable
Bolam 2019_AT	s	d	obj	48	54		Not estimable
Carayol 2019	s	d	sub	57	68	100.0%	0.17 [-0.16, 0.51]
Subtotal (95% CI)				**57**	**68**	**100.0%**	**0.17 [-0.16, 0.51]**
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.02 (P = 0.31)							





Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

* Intervention mode s: supervised; ns: not supervised
** Intervention timing d: during cancer therapy; a: after cancer therapy
*** Assessment of physical activity obj: objective; sub: subjective

Figure 28: Forest plots of the sensitivity analysis for the outcome moderate-to-vigorous physical activity (Goldschmidt et al. 2022)

8.2 Training maintenance after exercise interventions

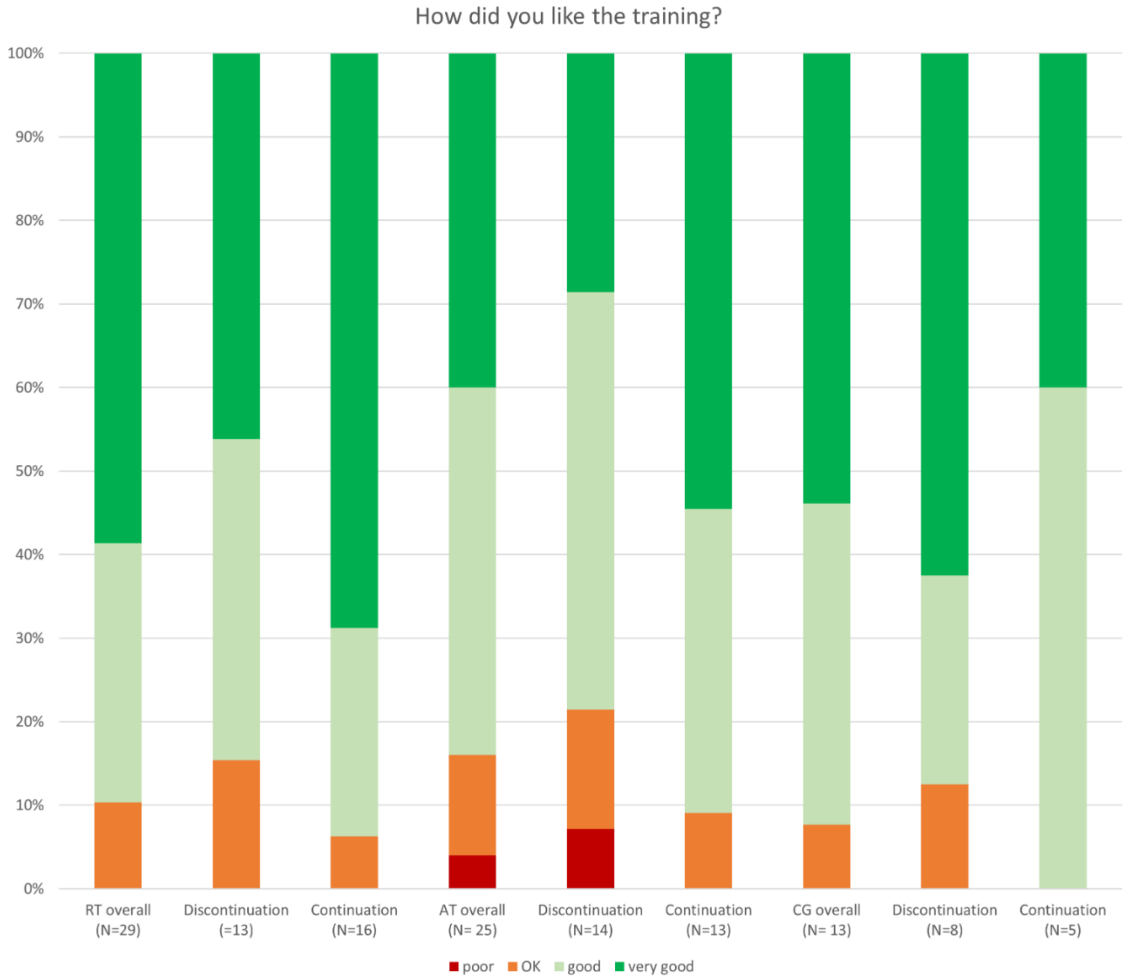


Figure 29: Plot presenting the rating of the training by group and by (dis)continuation (Goldschmidt et al. 2024a)

8.2.1 Questionnaires related to the training maintenance – Assessment of the training (dis)continuation; from the BENEFIT study (Goldschmidt et al. 2024a)

1. **How long did you continue your exercise after the end of the intervention?**
(independently of the location, i.e., the same or a different training facility)
   - o I still continue it (please continue with question 2)
   - o Not at all (please continue with question 3)
   - o Less than 1 month (please continue with question 3)
   - o At least 1 month, but less than 3 months (please continue with question 3)
   - o At least 3 months, but less than 6 months (please continue with question 3)
   - o At least 6 months, but less than 9 months (please continue with question 3)
   - o At least 9 months, but less than 12 months (please continue with question 3)
   - o At least 12 months, but less than 24 months (please continue with question 3)
   - o At least 24 months (please continue with question 3)

2. **If you still continue or continued the exercise for some time:**
What are/were your <u>three</u> main reasons?
Please indicate your 3 main reasons as following: Write "1" for the most important, "2" for the second most important reason and "3" for the third most important reason.

   (**Example**: ◊2 I enjoy the exercise ◊3 Personal contact with others ◊1 My health care professional advised me to do it)

◊ I enjoy the exercise
◊ I feel better after the exercise
◊ I notice that the exercise is physically good (e.g., physical performance improved, less pain, improved mobility)
◊ I notice that the exercise is psychologically good for me (e.g., better well-being, having a good feeling, relieving stress)
◊ I hope to reduce the probability for cancer recurrence or metastases
◊ Exercise is good for the health
◊ Personal contact with others during exercise are important to me
◊ Supervision through a trainer is important to me
◊ My health care professional advised me to do it
◊ My family or friends advised me to do it
◊ Other reasons (please specify): ______________________________
◊ Other reasons (please specify): ______________________________
◊ Other reasons (please specify): ______________________________

3. **If you don´t continue your exercise anymore:**
What are your <u>three</u> main reasons?
Please indicate your 3 main reasons as following: Write "1" for the most important, "2" for the second most important reason and "3" for the third most important reason.

(**Example**: ◊2 My family or friends advised me not to do it ◊3 I don´t see the point of the exercise ◊1 The distance to the training location is too long)

◊ Too expensive
◊ A lack of time /time expenditure too high
◊ Unsatisfied with supervision through trainer
◊ I don´t like the training location
◊ I don´t like the exercise
◊ The distance to the training location is too long
◊ I don´t see the point of the exercise
◊ I don´t enjoy the exercise
◊ I perform a different type of sport now → which: ______________________
◊ I don´t see any improvements
◊ No motivation
◊ My health care professional advised me not to do it
◊ My family or friends advised me not to do it
◊ Other reasons (please specify): ____
◊ Other reasons (please specify): ____
◊ Other reasons (please specify): ____

8.2.2 Questionnaires related to the training maintenance – Assessment of the training evaluation; from the BENEFIT study (Goldschmidt et al. 2024a)

The BENEFIT – study investigates different types and timing of exercise: Aerobic or resistance exercise training during neoadjuvant chemotherapy or resistance exercise training after the breast surgery.

1. **If you had been allowed to choose, which exercise would you have chosen at the start of the study?**
   - o Aerobic exercise training during the neoadjuvant chemotherapy
   - o Resistance exercise training during the neoadjuvant chemotherapy
   - o Exercising during the neoadjuvant chemotherapy, with no preference regarding aerobic or resistance exercise training
   - o Resistance exercise training after the breast surgery
   - o No preferences

2. How did you enjoy your training?

- o Very poor
- o poor
- o satisfactory
- o good
- o very good

4. **How did you perceive the following aspects of your training program?**

	Extremely negative	negative	Neither negative nor positive	positive	extremely positive
Contact to other patients?					
Contact to not affected persons?					
Personal approach/support through the trainer					
Training location					
Timing of the training					
Duration of the training					
Frequency of the training					
I don´t like the exercise					
Weekly ‘structure’ through two fixed training dates					
Being active					
Feedback regarding own performance capabilities					
Impact on the well-being					

4. What could we have improved for you?

(free text)

9 Publications

The present thesis was conducted as part of the BENEFIT study. The project members contributed differently to the publications, i.e., Prof. Dr. Karen Steindorf, Dr. Martina E. Schmidt, Prof. Dr. Friederike Rosenberger and Prof. Dr. Joachim Wiskemann were responsible for the study design, initiation and management as the principal investigators of the study. As a doctoral candidate, I contributed to the study by developing three questionnaires concerning the training evaluation, training maintenance and the impact of several complaints on the physical activity and exercise behavior. Additionally, I was responsible for screening and recruitment of eligible patients, study management, monitoring of the data quality, the conduction of the physical fitness tests using the Isomed 2000 to assess the isometric and isokinetic muscle strength of arms and legs, the cardiorespiratory fitness assessment with a Cardio Pulmonary Exercise Testing (spiroergometry) on a bicycle ergometer, and the assessment of the cognitive function. Furthermore, I was partly responsible for the identification of new suitable training facilities, the placement of the patients in the training facilities and the training adherence calls every other week to ensure a safe and effective training according to the patients' health status. The BENEFIT study was coordinated by previous researchers at different point in times, i.e., by Dr. Charlotte Kreutz, Dr. Jana Müller, Petra Armbrust, Marianne Förderer, and Christine Boos until 2017 and from 2017 to July 2020 solely by Dr. Charlotte Kreutz. I was solely responsible for the study from October 2020 until spring 2022 and was thereafter partly supported by the division's study nurse Bettina Rhein, who initially took over the screening and later conducted the anamnesis, the cognitive function tests and supported the training adherence calls. The placement of the patients to the training facilities was performed by myself, in consultation with Beate Biazeck from the network 'Onko Aktiv'.

The research topics of the publications were elaborated by Prof. Dr. Karen Steindorf, Dr. Martina E. Schmidt and myself. Accordingly, I analyzed the data and drafted the manuscripts in regular contact with my supervisors Prof. Dr. Karen Steindorf and Dr. Martina E. Schmidt. All project members read and approved the written manuscripts prior to its publication.

Previous publications related to the thesis of Dr. Charlotte Kreutz were not considered in the present thesis, because her topic included the sleep problems analyzed within the BENEFIT study, but were not related to the here presented topic of exercise attendance and training maintenance.

Publications related to this thesis

1. Goldschmidt S, Schmidt ME, Steindorf K. **Long-term effects of exercise interventions on physical activity in breast cancer patients: a systematic review and meta-analysis of randomized controlled trials.** Supp Care Cancer. 2023, 31:130. DOI: 10.1007/s00520-022-07485-6.

The first publication is related to the investigation of the sustainability of exercise interventions in terms of medium- and long-term physical activity and exercise behavior of breast cancer patients as presented in the results section 3.1 and discussed in section 4.1. My contribution encompasses the systematic literature search, data extraction, scoring of the risk of bias and the manuscript draft.

2. Goldschmidt S, Schmidt, ME., Rosenberger, F., Wiskemann, J., Steindorf, K. **Maintenance of aerobic or resistance training after an exercise intervention among breast cancer patients undergoing neoadjuvant chemotherapy.** Journal of Physical and Health. 2024, 21:1. Advance online publication. https://doi.org/10.1123/jpah.2023-0054.

The second publication is related to the investigation of 'Training maintenance and the reasons and possible influencing factors for (dis)continuation after exercise interventions' as presented in section 3.4 and discussed in section 4.3 and 4.4. My contribution entails the development of the questionnaire to assess the training maintenance, the data acquisition, data management, data analysis and drafting the manuscript.

3. Goldschmidt S, Schmidt ME, Rosenberger F, Wiskemann J, Steindorf K. **Patterns and influencing factors of exercise attendance of breast cancer patients during neoadjuvant chemotherapy.** Supportive Care in Cancer. 2024. Accepted on December 18, 2023.

The third publication is related to the investigation of 'Attendance at exercise interventions and its patterns and influencing factors' as presented in section 3.3 and discussed in section 4.2 and 4.4. My contribution covers the data acquisition, data management, data analysis and drafting the manuscript.

Other publications

Schmidt ME, Goldschmidt S, Hermann S, Steindorf K. **Late effects, long-term problems and unmet needs of cancer survivors.** Int J Cancer. 2022 Oct 15;151(8):1280-1290. doi: 10.1002/ijc.34152. Epub 2022 Jun 17. PMID: 35657637.

Goldschmidt S, Bauer N, Hacker V. **Telerehabilitation - Einsatzmöglichkeiten, Entwicklung und Wirksamkeit**. Sportphysio 2021; 9:75-81. DOI: 10.1055/a-1338-7491.

Oral presentations

Goldschmidt S, Schmidt ME, Steindorf K. (June 2022). **Langfristige Auswirkungen von supervidierten und nicht supervidierten Bewegungsinterventionen auf das körperliche Aktivitätsverhalten von Brustkrebspatientinnen**. 41. Jahrestagung der Deutschen Gesellschaft für Senologie. (DGS, Stuttgart) *Awarded with one of the best abstract prizes*

Poster presentations

Goldschmidt S, Schmidt ME, Steindorf K. (May 2022). **Maintenance of physical activity after exercise interventions: A systematic review and meta-analysis**. European Society of Medical Oncology Breast Cancer Congress (ESMO, Berlin)

Goldschmidt S, Schmidt ME, Steindorf K. (June 2022). **Maintenance of physical activity after exercise interventions: A systematic review and meta-analysis**. International PhD student cancer conference (IPSCC, Heidelberg)

Goldschmidt S, Schmidt ME, Steindorf K. (July 2022). **Maintenance of physical activity after exercise interventions: A systematic review and meta-analysis**. PhD retreat (DKFZ, Heidelberg).

Goldschmidt S, Schmidt ME, Steindorf K. (November 2022). **Maintenance of exercise beyond the end of a study intervention in patients with neoadjuvant breast cancer**. PhD Poster Session (DKFZ, Heidelberg).

Goldschmidt S, Schmidt ME, Rosenberger F, Wiskemann J, Steindorf K. (May 2023) **Nachhaltigkeit eines studienbasierten Ausdauer- oder Krafttrainings bei Brustkrebspatientinnen unter neoadjuvanter Chemotherapie.** Jahreskongress der Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie der Deutschen Krebsgesellschaft e.V. (AGSMO, online)

Goldschmidt S, Schmidt ME, Rosenberger F, Wiskemann J, Steindorf K. (July 2023) **Nachhaltigkeit eines studienbasierten Ausdauer- oder Krafttrainings bei Brustkrebspatientinnen unter neoadjuvanter Chemotherapie.** 42. Jahrestagung der Deutschen Gesellschaft für Senologie e.V. (DGS, Munich)

10 Curriculum vitae

PERSONAL INFORMATION

Name	Sarah Siri Goldschmidt
Date of birth	11 May 1994
Place of birth	Schwäbisch Gmünd
Nationality	German

EDUCATION

07/2020 – 01/2024	PhD student Division of Physical Activity, Prevention and Cancer German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg
10/2017 – 09/2019	Study of Health Sciences, Master of Science Technical University of Munich
10/2016 – 03/2019	Study of Exercise sciences, Master of Science Technical University of Munich
10/2013 – 09/2016	Study of Exercise sciences, Bachelor of Science Technical University of Munich
09/2005 - 07/2013	Secondary school Internat und Heimschule St. Landolin, Ettenheim and Kolleg St. Blasien, St. Blasien

ACADEMIC AND PROFESSIONAL DEGREES

30/09/2019	Master of Science Health Science- Prevention and Health Promotion Technical University of Munich
01/07/2019	Master of Science Diagnostics and Training Technical University of Munich
12/08/2016	Bachelor of Science Scientific Foundations of Sports (Wissenschaftliche Grundlagen des Sports)Technical University of Munich
01/07/2013	Abitur Kolleg St. Blasien, St. Blasien
12/07/2010	Mittlere Reife Internat und Heimschule St. Landolin, Ettenheim

11 Acknowledgements

I would like to take this opportunity to express my sincere thanks and gratitude to very important and supportive people in my life, without whom the present thesis would not exist.

Cordial thanks belong to Prof. Dr. Karen Steindorf for the opportunity, facilitation and supervision of this thesis. I appreciate her great empathetic support, patience and valuable feedback throughout my time as a doctoral researcher.

Sincere thanks to Dr. Martina E. Schmidt for her great and continuous empathetic support, time and patience in everyday questions and valuable co-supervision of my work.

Many thanks to Prof. Dr. Friederike Rosenberger and Prof. Dr. Joachim Wiskemann for the good cooperation within the performance diagnostics related to the BENEFIT study.

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This thesis would not exist without supportive patients. I appreciate and thank every patient, who participated in the BENEFIT study and, thus, contributed to this thesis. A great thank for the support.

Above all, I cordially thank my beloved family and friends, who always covered my back through their continuous mental support and motivation. Thank you for believing in me, encouraging and supporting me! Without you, I really would not have made it.
I'd also like to thank several important people, who supported me in various phases of my life and, therefore, enabled me to be who I am, and achieve what I achieved. Thank you very much indeed.

12 Eidesstattliche Erklärung

1. Bei der eingereichten Dissertation zu dem Thema

Exercise interventions for breast cancer survivors - Investigations of attendance and of short- and long-term effects on the exercise and physical activity behavior of breast cancer survivors

handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

3. Die Arbeit oder Teile davon habe ich bislang nicht an einer Hochschule des In- oder Auslands als Bestandteil einer Prüfungs- oder Qualifikationsleistung vorgelegt.

4. Die Richtigkeit der vorstehenden Erklärungen bestätige ich.

5. Die Bedeutung der eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unrichtigen oder unvollständigen eidesstattlichen Versicherung sind mir bekannt. Ich versichere an Eides statt, dass ich nach bestem Wissen die reine Wahrheit erklärt und nichts verschwiegen habe.

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