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Aerobic fitness in late adolescence and the risk of cancer and cancer-associated mortality in adulthood: A prospective nationwide study of 1.2 million Swedish men

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ABSTRACT

Background: The incidence of cancer has steadily risen. It is important to identify modifiable predictors in early life that may decrease cancer risks and mortality. The present study aims to investigate the relationship between aerobic fitness in adolescence and the subsequent risk of cancer and cancer-associated mortality.

Methods: The study included 1 185 439 Swedish men born between 1950 and 1980 that participated in the military conscription (mean age = 18 years). The results from the aerobic fitness test (W_{max}) was linked to the risk of cancer and cancer-associated mortality during a 40-years' follow-up using Cox proportional hazards models. A co-sibling design was employed to take familial factors into account.

Results: During a mean follow-up of 27 years 15 093 cases of cancer and 4900 cancer-associated mortalities were registered. Higher W_{max} (per additional 1 SD) was associated with a decreased risk of cancer at 40 years of follow-up (HR 0.93; 95% CI 0.91–0.96 for cancer and HR 0.82 95% CI 0.76–0.87 for cancer-associated mortality) but not at 5 years of follow-up (HR 1.03; 95% CI 0.99–1.07; and HR 1.04; 95% CI 0.97–1.12). In the co-sibling model the protective effects of high W_{max} were increased at 40 years of follow-up for cancer (HR 0.91; 95% CI 0.85–0.98) and cancer-associated mortality (HR 0.78; 95% CI 0.68–0.89).

Conclusions: These findings identify in late adolescence a potentially modifiable predictor of cancer, with higher aerobic fitness associated with a decreased risk of cancer incidence and mortality later in life.

1. Introduction

Cancer is the second most common cause of death and a leading contributor to serious morbidity, and the incidence of malignant neoplasms is projected to increase by 70% in the coming 20 years [1]. Long-term risk assessments for both cancer incidence and mortality are therefore of great importance, as well as the identification of modifiable factors early in life that may reduce subsequent cancer risk and mortality. Aerobic fitness is a powerful and potentially modifiable marker of health, and a high level of fitness is associated with a reduced risk of multiple diseases and all-cause mortality [2,3]. High levels of aerobic fitness also have been associated with large risk reductions for cancer incidence and cancer-associated mortality [4–7]. Those who are aerobically fit and are diagnosed with cancer also have an increased rate of survival [8].

The association of aerobic fitness with cancer has primarily been investigated in middle-aged and older populations [6]. In such settings, underlying diseases may lead to problems with residual confounding and reverse causation, distorting the observed associations. In addition, as most study populations consist of middle-aged individuals, they fail to include cancers of young adulthood or examine potentially modifiable predictors at younger ages. It is also important to take familial factors into account in risk assessments over the life-course, as the genetic components of aerobic fitness and cancer are both large [9–11].

The purpose of the current study is to overcome several limitations in previous studies and explore the association between aerobic fitness early in life and the risk of cancer and cancer mortality in young adulthood as well as later in life. To achieve this, we used the

Abbreviations: W_{max}, Watt max; SD, standard deviation; HR, hazard ratio

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nationwide Swedish military conscription registry that provides reliable data on aerobic fitness and anthropometrics for young conscripting males, and linked the aerobic fitness data with subsequent cancer and cancer-associated mortality. We also employed a co-sibling analysis that permits an assessment of the degree to which observed associations between aerobic fitness and cancer are confounded by familial (genetic and/or shared environmental) factors. The current study adds to previous literature by including a young, largely unselected and nationwide population that has reliable measurements of fitness, employing a co-sibling design and performing a long follow-up.

2. Materials and methods

2.1. Study population

This prospective cohort study was based on Swedish population-based registers with national coverage. Several different registers were linked using each person's unique identification number. To preserve confidentiality, this ID number was replaced by a serial number. The population considered for inclusion in the present study consisted of all Swedish men born between the years 1950 and 1980 (n = 1 728 232). These individuals were further selected by including those who participated in the military conscription. During the selected years military conscription was virtually mandatory and exemption was only granted for individuals with a severe medical condition, or who were incarcerated. Conscription status and results of the conscription examinations were gathered from the Military Conscription Registry. Of the original 1 728 232 individuals 82.4% (1 423 926) from the original population partook in the conscription process. Further inclusion criteria were applied with height (> 140 cm and < 215 cm), weight (> 40 kg and < 160 kg) and aerobic fitness (> 100 W [W] and < 999 W) requirements; subjects with missing data on these measurements were also excluded. For the first three years of conscription, i.e. 1969 to 1972 W_{max} testing was not yet part of the standard testing regimen – although some were tested – leading to almost all conscripts being excluded for those particular years. In total, 1 185 439 eligible participants (68.6% of original population) were included in the study.

2.2. Baseline examination

The military conscription consisted of an initial two-day, highly standardized testing regimen. The process has been described previously [12]. Anthropometric measurements were collected: weight on a standardized kilogram scale and height using a wall-mounted gauge. The potential recruits underwent a test for aerobic fitness on an electrically braked ergometer cycle. Briefly, a resting ECG was registered, and if normal, the testing proceeded with 5 min warm up with a weight-adjusted resistance (75–150 W). After warm-up, resistance on the bike was increased with 1-W increments with a pace of 25 W per minute until the subject could no longer continue due to fatigue or other symptoms. The resistance at which the subject failed was registered as the peak aerobic fitness level (W_{max}).

2.3. Data collection during follow-up

Information on cancer diagnosis during follow-up was gathered from the National Hospital Discharge Registry that is maintained by the National Board of Health and Welfare. The diagnoses in the registry have a positive predictive value of 85–95 % [13]. Seventeen subgroups of cancer types were used based on the most common forms of cancer in the male population, including prostate cancer, lung and bronchial cancers, colorectal cancers, skin cancer, Hodgkin's and Non-Hodgkin's lymphoma (separate groups), renal cancer, head-neck cancer, cancers of the central nervous system, pancreatic cancer, cancer of the liver, bile duct and gallbladder, bladder cancer, stomach cancer, myeloma, thyroid cancer and leukemia. The pertaining ICD codes (version 8, 9 and 10) are supplied in Supplementary Table 1. Date and cause of death were retrieved from the National Cause of Death Registry during the entire follow-up. Furthermore, deaths caused by cancer (here referred to as cancer-associated mortalities) were retrieved according to the categorization of cancer diagnoses outlined in Supplementary Table 1. The study participants were followed from conscription to either the date of cancer diagnosis, date of death, date of emigration or December 31st 2012, i.e., at the end of follow-up.

2.4. Statistical analysis

The distribution and skewness of continuous variables were checked graphically using histograms. W_{max} was expressed as a Z-score standardized to 0 with a standard deviation set to 1, created for each year of conscription, the rationale being that (1) the mean W_{max} gradually increased during the years of conscription, and (2) the testing protocol was slightly altered (with larger increments being used during the early years). The relationship between W_{max} and the later risk of cancer and cancer-associated mortality was analyzed using Cox proportional hazards models. Follow-up time (in number of years) was measured from year of conscription until first registration for cancer, death, or emigration – whichever came first. For each outcome (cancer and cancer mortality) model 1 only included W_{max} as the exposure variable. In the models, we investigated the proportionality assumption by letting the effect of W_{max} vary by follow-up time. We conducted several different models and selected the model with the best fit (lowest AIC). This model (henceforth referred to as Model 1) included an interaction term between W_{max} and follow-up time. We illustrate the violation of the proportionality assumption by calculating the Hazard Ratio for W_{max} at different time points (1, 5,10, 20, 30 & 40 years). The interaction term was added to all later Cox's proportional hazards models. In model 2 we included year of conscription and Body Mass Index. Year of conscription was added to adjust for cohort effects and for possible adjustments of testing procedures, although the previously described standardizations likely accounted for most of that effect. BMI was added to adjust for the positive effect of increasing bodyweight on W_{MAX}, and for its association to cancer [14]. Next, we sought to assess the degree to which the results from these regression models reflect confounding by familial risk factors (either genetic or environmental) using a co-sibling design. Using the Swedish Multi-Generation Register, we identified all full-sibling sets within the conscription cohort. Using stratified Cox proportional hazards models, allowing for a different baseline hazard for all unique sets of siblings, we refit all analyses within each strata in which the siblings within the strata differed in their W_{MAX}. This allows us to contrast the rates of cancer and cancer associated mortality in siblings with different levels of W_{MAX}. The HR is then adjusted for the familial cluster, and, therefore, accounts for an array of unmeasured genetic (full siblings share on average 50% of their genes identical by descent) and environmental factors shared within the sibling pair [15]. For statistical analyses the software Statistical Analyses System (SAS, version 9.4, SAS Institute Inc., Cary NC, USA) was used.

The regional ethics committee of Lund University approved the current study.

3. Results

3.1. Baseline characteristics

The baseline characteristics for the study cohort including those with a later diagnosis of cancer and cancer-associated mortality are presented in Table 1. Individuals who received a cancer diagnosis during follow-up had on average about 20 W lower W_{max} compared to those who did not receive a diagnosis, while those who died of cancer had on average about 25 W lower W_{max}, roughly equating to 0.5 standard deviations (mean W_{max} 278 W). The distributions of aerobic fitness and BMI are presented in Fig. 1A and B and were determined as

Table 1
Descriptive statistics according to later cancer diagnosis or death associated with cancer. Values are presented as means ± their standard deviation (SD).

Variable	All	Cancer diagnosis (n = 15,093)	Cancer-associated mortality (n = 4900)
Body Mass Index (kg/m^2)	21.8 ± 2.9	21.8 ± 2.9	21.8 ± 3.1
W_{max} (Watt)	278 ± 53	258 ± 48	253 ± 47

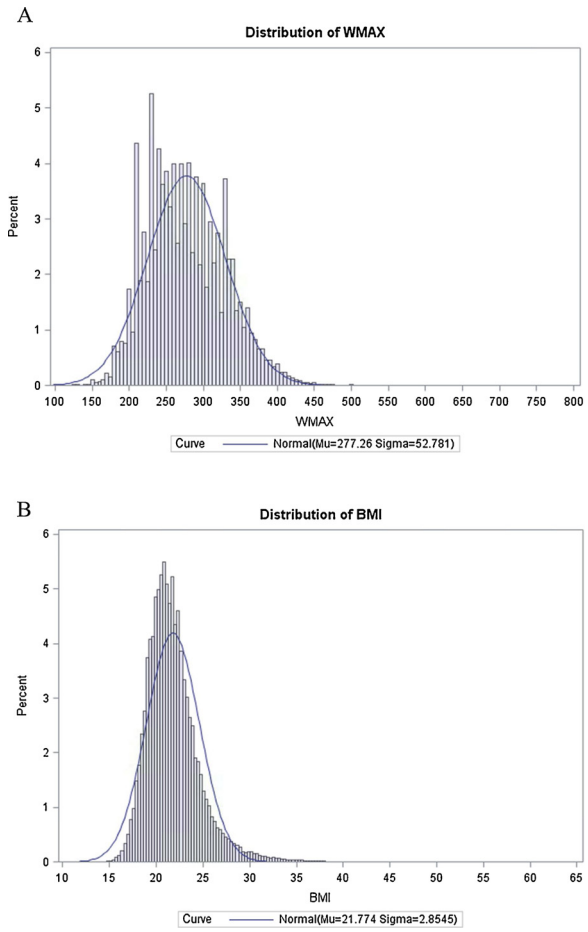

Fig. 1. A and B: the distribution of W_{max} and BMI.

normally distributed.

3.2. Frequency of endpoints during follow-up

The number of cases of cancer and cancer-associated mortality for each 5-year period of follow-up are shown in Table 2. A total of 15 093 cases of cancer within the 17 categories were diagnosed after a mean of 24.4 ± 10.4 years from conscription. 4900 cancer-associated mortalities were recorded after a mean of 25.6 ± 9.5 years from conscription. The number of cancers and cancer-associated mortalities for each 5-year period of follow-up are also presented in Fig. 2. The number of both cancers and cancer-associated mortalities per five-year period increased over time, with a marked increase after 30 years of follow-up. The five most common types of cancers during the follow-up were prostate cancer, colorectal cancer, cancer of the central nervous system, skin cancer and Non-Hodgkin's lymphoma. For cancer-associated deaths, the five most common types were cancers of the central nervous system, colorectal cancer, bronchi and lung cancer, skin cancer and leukemia (data not shown).

Table 2
The number of cancer cases and cancer-associated mortalities for each five-year period during follow-up.

Time interval	No. of cancer cases	No of cancer deaths
≤ 5 years	858	157
> 5 to ≤ 10 years	1112	285
> 10 to ≤ 15 years	1411	383
> 15 to ≤ 20 years	1689	558
> 20 to ≤ 25 years	2041	738
> 25 to ≤ 30 years	2556	919
> 30 years	5426	1860
Total	15,093	4900

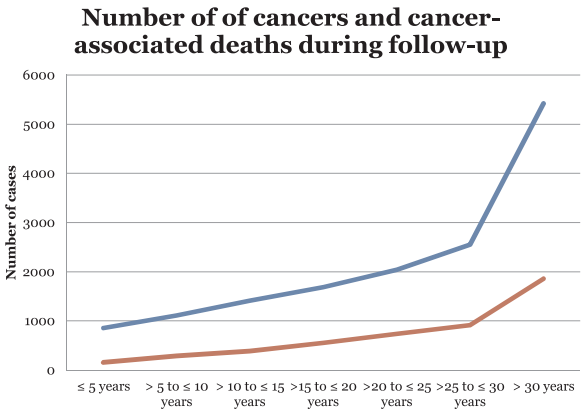

Fig. 2. The number of cases of cancers and cancer-associated mortalities for the five-year intervals of follow-up.
The blue line represents the number of new cases of cancer diagnosis in the population while the red line represents the number of cancer-associated mortalities.

3.2.1. Cox proportional hazard analyses

The univariate, multivariate and co-sibling Cox proportional hazards models for the association between aerobic fitness at baseline and the later risk of cancer and cancer-associated mortality are presented in Table 3. In the univariate model (Model 1), each increase of one standard deviation (SD) of W_{max} was associated with a 5% decrease in the risk of cancer (Hazard ratio [HR] 0.95; 95% CI 0.93 – 0.98) and a 16% decrease in the risk of cancer-associated mortality (HR 0.84; 95% CI 0.80 – 0.89) at 40 years of follow-up, corresponding to a mean age of 58 years. At five years of follow-up, corresponding to a mean age of 23 years, an opposite association was observed: here each increase in one SD of W_{max} was instead associated with a 5% increase in the risk of cancer (HR 1.05; 95% CI 1.02–1.11) and a 7% increased risk of cancer-associated mortality (HR 1.07, 95; % CI 1.00–1.15). Adding covariates (Model 2) resulted in slightly reduced risk estimates, and confidence intervals crossed 1 for both outcomes.

3.2.2. Co-sibling analyses

In the co-sibling models a strata for full sibling status was entered into the Cox model. 226 287 individuals had at least one full sibling that also conscripted. Given the wide range of results on the W_{max} test (> 100 to 800) we assumed they were all discordant for aerobic fitness. In 5718 cases of cancer, there was a discordance between siblings (i.e. no sibling had been diagnosed with cancer); for cancer-associated death

Table 3
Cox proportional hazards model for W_{max} at baseline and the risk of cancer and cancer-associated mortality later in life with the effect of W_{max} varying by follow-up time. In Model 1 the univariate association between W_{max} and the outcome was tested using the interaction term between aerobic W_{MAX} and follow-up time (for specified points during follow-up). In Model 2 BMI and year of conscription were added. In Model 3 a co-sibling design was used, where a stratification term for all full siblings was added. In Model 4 a co-sibling model was used, with the addition of the covariates in Model 2.

	Cancer diagnosis		Cancer-associated mortality	
Time	Estimate (HR)	95 % CI	Estimate (HR)	95 % CI
Model 1				
(*n* = 1,185,439)				
1 year	1.06	1.02 – 1.11	1.10	1.01 – 1.19
5 years	1.05	1.01 – 1.09	1.07	1.00 – 1.15
10 years	1.04	1.01 – 1.07	1.03	0.98 – 1.09
20 years	1.01	0.99 – 1.03	0.97	0.94 – 1.00
30 years	0.98	0.96 – 1.00	0.91	0.88 – 0.94
40 years	0.95	0.93 – 0.98	0.84	0.80 – 0.89
Model 2				
(*n* = 1,185,439)				
1 year	1.04	1.00 – 1.09	1.07	0.99 – 1.17
5 years	1.03	0.99 – 1.07	1.04	0.97 – 1.12
10 years	1.02	0.98 – 1.05	1.01	0.95 – 1.07
20 years	0.99	0.97 – 1.01	0.94	0.91 – 0.97
30 years	0.96	0.94 – 0.98	0.88	0.85 – 0.91
40 years	0.93	0.91 – 0.96	0.82	0.76 – 0.87
Model 3				
(*n* = 1,167,990)				
1 year	1.00	0.92 – 1.07	1.08	0.91 – 1.28
5 years	0.99	0.93 – 1.06	1.04	0.91 – 1.21
10 years	0.98	0.93 – 1.03	1.00	0.90 – 1.12
20 years	0.96	0.93 – 0.99	0.93	0.87 – 0.99
30 years	0.94	0.90 – 0.99	0.85	0.79 – 0.92
40 years	0.92	0.86 – 0.99	0.79	0.68 – 0.90
Model 4				
(*n* = 1,167,990)				
1 year	0.99	0.91 – 1.07	1.06	0.89 – 1.26
5 years	0.98	0.92 – 1.05	1.03	0.89 – 1.19
10 years	0.97	0.92 – 0.99	0.99	0.88 – 1.11
20 years	0.95	0.92 – 0.99	0.91	0.85 – 0.98
30 years	0.93	0.89 – 0.98	0.84	0.77 – 0.91
40 years	0.91	0.85 – 0.98	0.78	0.68 – 0.89

the corresponding number was 1895. In the univariate co-sibling model (Model 3) the association between W_{max} and the risk of cancer and cancer death was calculated.

At 40 years of follow-up the inverse association between W_{max} and cancer risk or cancer-associated mortality was even stronger than in Model 1: each increase in one SD of W_{max} was associated with an 8% decrease in the risk of cancer (HR 0.92; 95% CI 0.86 – 0.99) and a 21% decrease in the risk of cancer-associated mortality (HR 0.79; 95% CI 0.68 – 0.90). I.e., when accounting for familial factors, the decrease in risk of cancer and cancer-associated mortality associated with a higher aerobic fitness appeared to decrease slightly further. At five years of follow-up the hazard ratio approached 1 for both cancer (HR 0.99; 95% CI 0.93 – 1-06) and cancer-associated mortality (HR 1.04; 95% CI 0.91–1.21), in contrast with the findings of Model 1. This means that the increased risk of cancer and cancer-associated mortality at 5 years of follow-up for those with higher W_{max} in Model 1 was no longer present when taking familial factors into account. Including individual covariates (Model 4) had little effect on the results.

4. Discussion

This nationwide cohort study of 1.2 million Swedish men examined the association between aerobic fitness in late adolescence and the subsequent risk of cancer and cancer-associated mortality. In line with previous studies, we found that a high aerobic fitness at baseline was associated with a decreased risk for cancer and cancer-associated mortality during middle age. High aerobic fitness appeared to have a greater impact on the risk of cancer-associated mortality compared to the risk of cancer diagnosis. For the early years of follow-up, a high aerobic fitness was associated with an increased or unaffected risk of both endpoints. However, the co-sibling analyses showed that the association at the early years of follow-up seemed to be entirely confounded by familial factors.

The contribution of the present study is the use of a large, nationwide cohort with a long follow-up period, validated endpoints and the opportunity to employ a co-sibling design to take familial factors such as genetic factors and a shared environment into account. The main results are in line with previous studies. For example, Lee and colleagues found a strong, inverse relationship between level of aerobic fitness and cancer mortality in middle age [16]. Similarly, Lakoski et al. found that individuals with high aerobic fitness were at a lower risk of cancers of the lung and gastrointestinal tract compared to their less fit counterparts, also in a middle-aged population [8].

As mentioned above, we assessed the effect of W_{max} on cancer and cancer-associated mortality for specified time points. This revealed a difference over time: during the first half of the follow-up, i.e., when subjects were aged 18–38 years, high aerobic fitness was either not associated with the risk of cancer or cancer mortality, or it conferred a slightly increased risk. Importantly, this association was attenuated when accounting for familial factors, indicating a confounding by familial factors. Conversely, high aerobic fitness was associated with a decreased risk of cancer and cancer mortality during the second half of the follow-up. This trend may be attributable to the varying share of cancer types for different age groups, as cancers of young adulthood – and thusly those that likely occurred during the first half of the follow-up – are primarily comprised of lymphomas, leukemia and tumors of the central nervous system [17,18]. Robsahm et al. investigated the relationship between aerobic fitness and the risk of site-specific cancers

and found no association between level of fitness and the risk of hematological malignancies or tumors of the central nervous system [19]. In contrast, aerobic fitness has been linked to cancers typically diagnosed during and past middle age – predominantly comprised of solid tumors, especially of the lungs and gastrointestinal tract [4,20–22].

The mechanisms behind the observed associations are unknown. As aerobic fitness is to a large degree a heritable trait, genetic factors are likely involved [10]. For example, the IGF-2 and VEGF genes are involved in both aerobic fitness and cancer development [23–26]. However, a significant share (at least 35%) of aerobic fitness can still be attributed to behavioral differences, and physical activity is associated with a lower risk of cancer, in particular solid tumors of the prostate gland, lungs and colon [10,27]. With respect to cancer mortality, high aerobic fitness is associated with a lower mortality in those diagnosed with common forms of cancer [28]. Furthermore, physical activity – which in turn may increase aerobic fitness – is associated with an increased cancer survival [29]. As for cancer incidence, physical activity leading to higher aerobic fitness likely contributes to a lower risk of developing cancer through mechanisms affecting systemic inflammation, oxidative stress and the immune system, among others [30]. It is unknown to what extent genetic factors contribute to the association between aerobic fitness and cancer incidence.

The current study has several weaknesses that warrant discussion. Firstly, this is an observational study; therefore precaution is warranted concerning assumptions of causality, although the co-sibling analysis allows for an “adjustment” of familial factors. Secondly, it included only men; therefore the results are not necessarily applicable to women. Thirdly, the study lacked several important covariates, including smoking, although the co-sibling design might account for some of the smoking status, given the strong influence of shared environment on smoking [31]. Some of the covariates not included, namely smoking, dietary habits and physical activity may in turn influences aerobic fitness [32]. Although their inclusion would have been valuable, they were not available to us. Also, we used BMI as a measurement of obesity, with its inherent drawbacks. This is of importance, as there may be a discrepancy in the relationship to cancer for measurements of general and site-specific obesity [33]. The long follow-up time can also be considered a weakness as the level of fitness may have changed over time, and we were unable to assess such changes. Whether aerobic fitness and physical activity is stable over time has also been debated [34–36] but the association between aerobic fitness early in life and various diseases during the lifespan remains strong and consistent across studies, despite adjustment for important confounders [37,38]. Finally, and as discussed above, the follow-up time was limited for the youngest cohorts, which means that the study was unable to include all lifetime cases in this subgroup. However, the present study included a large number of young conscripts, who we were able to follow until 61 years of age, which represents a novel contribution as most previous studies were only able to include baseline data on middle-aged men. The strengths of the present study include a large, nationwide cohort with valid measurements of aerobic fitness and endpoints, with a long follow-up and the possibility to take familial factors into account.

5. Conclusion

A higher aerobic fitness in late adolescence is associated with a decreased risk of cancer and cancer-associated death during later years of follow-up (around middle age) but not during early years of follow-up. Importantly, this study sheds light on the association between aerobic fitness in late adolescence and subsequent risk of cancer and cancer-associated death. Furthermore, the results advance our knowledge of the relevance of aerobic fitness for cancer prevention, particularly its usefulness early in life as a potentially modifiable risk factor for cancer and cancer-associated mortality in men across the life course.

Author statement

GH, HO, CC, KS and JS conceived the idea for the study. All authors helped to plan and shape the research. GH and HO performed the statistical analyses with input from all other authors. All authors helped to interpret the results. GH wrote the manuscript. All authors have read the manuscript and provided feedback and approved the final version. KS and JS supervised the project.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.01.012.

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