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Modeling the cumulative benefits of regular physical activity on type 2 diabetes progression

Pierluigi Francesco De Paola [a,b,c], Alessandro Borri [c,*], Fabrizio Dabbene [b], Karim Keshavjee [d], Pasquale Palumbo [e], Alessia Paglialonga [f]

[a] Polytechnic of Bari, Bari, 70126, Italy
[b] CNR-IEIIT, Torino, 10129, Italy
[c] CNR-IASI, Roma, 00185, Italy
[d] University of Toronto, Dalla Lana School of Public Health, Institute of Health Policy, Management and Evaluation, Toronto, Canada
[e] University of Milano-Bicocca, Department of Biotechnologies and Biosciences, Milan, 210126, Italy
[f] CNR-IEIIT, Milan, 20133, Italy

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ABSTRACT

Despite the well-acknowledged benefits of physical activity for type 2 diabetes (T2D) prevention, the literature lacks validated models able to predict the long-term benefits of exercise on T2D progression and that could be used to support personalized risk prediction and prevention. To bridge this gap, we developed a novel mathematical model that formalizes the link between exercise and short- and long-termglucose–insulin dynamics to predict the benefits of regular exercise on T2D progression. Specifically, we combine a well-known T2D progression model that describes a fast dynamics of physical activity with a slow dynamics that accounts for the cumulative effects of regular physical activity on pancreatic beta-cell mass and on individual insulin sensitivity, mediated by the integral effect of interleukin-6 produced during exercise. The model was used to estimate the benefits of physical activity in four conditions: (i) regular exercise of varying intensity; (ii) regular exercise following the World Health Organization (WHO) recommendations for chronic disease prevention; (iii) discontinuation of a regular exercise program; and (iv) assessment of the inter-individual variability in a wide range of simulated scenarios. These results are encouraging and can set the basis for future development of decision support tools able to assist patients and clinicians in tailoring preventive lifestyle interventions. Results showed that the model quantitatively captured the dose–response relationship (larger benefits with increasing intensity and/or duration of exercise), it consistently reproduced the benefits of clinical guidelines for diabetes prevention, and it accurately predicted persistent benefits following interruption of physical activity, in line with real-world evidence from the literature.

1. Introduction

Type 2 diabetes (T2D) is a high-prevalence, high-burden chronic disease, whose impact is becoming increasingly concerning for public health worldwide [1]. Estimations forecast a growing burden on the healthcare systems, with the global prevalence projected to increase up to 592 millions by 2035 [2–4]. However, substantial evidence suggests that T2D can be prevented, for example through lifestyle interventions including physical activity [4–10].

Mathematical models can be helpful to quantitatively predict the benefits of lifestyle interventions on T2D progression and can provide a basis for reducing the individual risk through tailored recommendations for T2D prevention. For example, predictive models able to estimate the risk of T2D as a function of individual health status and lifestyle on a daily basis may be integrated into digital patient monitoring tools to continuously track individual biomarkers and support patients in achieving targets and reduce their risk through behavior change [11–14]. Several mathematical models were introduced in the literature to describe the slow dynamics of T2D progression in the long term as a function of, e.g., individual blood glucose levels, insulin concentration, or mass of pancreatic beta-cells [15–18]. These models are well-established and show promise for predicting the risk of developing T2D along a time span of several years. However, they do not include mechanistic descriptions of the long-term beneficial effects of exogenous interventions, for example physical activity, on

* Correspondence to: National Research Council of Italy, CNR-IASI, via dei Taurini 19, 00185, Rome, Italy.
E-mail addresses: p.depaola@phd.poliba.it (P.F. De Paola), alessandro.borri@iasi.cnr.it (A. Borri), fabrizio.dabbene@cnr.it (F. Dabbene), karim.keshavjee@utoronto.ca (K. Keshavjee), pasquale.palumbo@unimib.it (P. Palumbo), alessia.paglialonga@cnr.it (A. Paglialonga).

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T2D risk. Regarding the effects of physical activity, most of the models introduced so far are focused on the short-term effects of exercise, on a timescale of minutes to hours [19–22]. Hence, the available models of the short-term effects of physical activity are suitable to be employed in short-range closed-loop glucose control techniques, whose effectiveness has been shown in several works [23–26]. However, these short-term models are not able to quantitatively describe the cumulative beneficial effects of repeated exercise sessions on the slow dynamics of T2D progression — effects that are known to occur on a timescale of weeks, months, or even years [9,27,28].

As a first step to address this research gap, in a recent exploratory work [29] we developed a preliminary version of a two-timescale model by combining a well-established model of long-term T2D progression [16] with (i) a model of the short-term effects of individual sessions of physical activity [21] and (ii) an approximate model of the long-term, cumulative effects of repeated sessions of physical activity mediated by Interleukin-6 (IL-6), a protein with anti-inflammatory action released by muscle tissue under exercise [30] that contributes in preserving beta-cell mass and function [27,28,30]. Specifically, we modeled the release of IL-6 induced by physical exercise as suggested by Morettini et al. [30] and we described the integral, cumulative effect of IL-6 released during repeated exercise sessions by introducing an additional state variable that represents the total volume of IL-6 and acts on the balance between beta-cell proliferation and apoptosis, therefore regulating insulin release and glucose metabolism. The preliminary model proposed in [29] was able to consistently predict an overall increase in beta-cell mass (and, therefore, an increase in insulin concentration) following regular physical activity, leading to a decrease in basal glucose levels. However, the model did not account for the effects of varying intensity and duration of physical activity on beta-cell proliferation and apoptosis and did not include the benefits of physical activity on individual insulin sensitivity.

In pursuit of the ultimate goal of developing and validating a mathematical model capable of accurately predicting the benefits of physical activity for T2D risk monitoring and prevention, the aim of this study is to further develop the abovementioned, preliminary two-timescale model and assess its ability to describe real-world evidence on the benefits of different programs of physical activity, as available from the literature and from preventive recommendations. Specifically, in this study:

(i) we modify the model in [29] to incorporate the influence of varying physical activity on beta-cell proliferation and apoptosis and on insulin sensitivity and, in turn, on glucose–insulin dynamics;

(ii) we investigate if, and to what extent, the model predictions are aligned with real-world evidence. Specifically, we assess the predictions of the model by considering different time courses of T2D progression (i.e., different time constants of the simulated decay in insulin sensitivity) in a range of simulated conditions: different exercise programs at varying intensity and weekly duration, different World Health Organization (WHO) recommendations for chronic disease prevention [31], and the effect of de-training, as reported in different diabetes prevention programs [7,32]; moreover, we assess the predictions of the model when accounting for inter-individual variability in a broad spectrum of simulated conditions.

2. Methods

2.1. Model formulation

The main equations of the proposed model are reported in the followings:

$$\bar{P}(ISR) = P(ISR)\cdot\left(1+\zeta_1\frac{V_l^2}{k_n^2+V_l^2}\right), \tag{1a}$$

$$\bar{A}(M) = A(M)\cdot\left(1-\zeta_2\frac{V_l^2}{k_n^2+V_l^2}\right), \tag{1b}$$

$$\dot{\beta} = \frac{\bar{P}(ISR)-\bar{A}(M)}{\tau_\beta}\beta, \tag{1c}$$

$$\dot{S}_I = \frac{-(S_I - S_{I,target})}{\tau_{SI}}\cdot\left(1-\zeta_3\frac{V_l}{k_{n,si}+V_l}\right), \tag{1d}$$

$$\dot{PVO}_2^{\max} = -0.8\,PVO_2^{\max} + 0.8u, \tag{1e}$$

$$\dot{IL}_6 = SR\cdot PVO_2^{\max} - K_{IL6}\cdot IL_6, \tag{1f}$$

$$\dot{V}_l = IL_6 - k_s V_l, \tag{1g}$$

$$\dot{G} = R_0 + \frac{W}{V_g}\left(G_{prod}-G_{up}\right) - \left(E_{g0}+S_I I\right)G, \tag{1h}$$

$$\dot{I} = \frac{\beta}{V}ISR - kI - I_e, \tag{1i}$$

$$\dot{\gamma} = \frac{\gamma_\infty(G)-\gamma}{\tau_\gamma}, \tag{1j}$$

$$\dot{\sigma} = \frac{\sigma_\infty(ISR,M)-\sigma}{\tau_\sigma}, \tag{1k}$$

where $\zeta_1 = 10^{-4}$, $\zeta_2 = 10^{-4}$, $k_n = 10^6$ (pg/ml)*min, $\zeta_3 = 1.4$, $k_{n,si} = 5\cdot 10^6$ (pg/ml)*min. Physical activity is captured through the state variable $PVO_2^{\max}$, representing the *sovrabasal* oxygen consumption during exercise as a function of the exercise intensity u (Eq. (1e)). The variable $PVO_2^{\max}$, in turn, promotes the dynamics of G_{prod}, G_{up} and I_e (describing the short-term impairment of blood glucose regulation induced by the exercise as described in our previous work [29]), and the dynamics of IL_6, that is released by muscle tissues under exercise (short-term) and exerts its integral anti-inflammatory action (long-term), as expressed by the state variable V_l representing the cumulative effect of IL_6 (Eqs. (1f)–(1g)). As discussed in [29], in our modeling framework, IL-6 is not intended to represent the entire spectrum of biological mechanisms, but rather it serves as a physiologically grounded agent that triggers downstream processes. These complex physiological effects, including anti-inflammatory responses and metabolic pathways, are synthetically encoded in the model via the state variable V_l. This approach allows to capture the cumulative impact of physical activity on metabolic health in a compact form, while maintaining a reasonable trade-off between biological detail description and computational complexity. For a complete description of variables and parameters reference is made to Appendix. To model the influence of varying physical activity on beta-cell dynamics, in this study a multiplicative contribution is introduced in Eqs. (1a) and (1b) in place of the additive contribution originally used [29] to scale the effect of the exercise with respect to natural beta-cell proliferation ($\bar{P}(ISR)$) and apoptosis ($\bar{A}(M)$). Similarly, a multiplicative factor is added to insulin sensitivity S_I (Eq. (1d)) to account for the improvement of S_I due to regular physical activity, as reported in [33,34].

As a result, in the proposed model higher values of V_l due to increased physical activity lead to an improvement of S_I and an increase of beta-cell mass (β) due to increased proliferation ($\bar{P}(ISR)$) and reduced apoptosis ($\bar{A}(M)$) leading, in turn, to an increase in basal insulin concentration (I) (Eq. (1j)) and a decrease in basal glucose concentration (G) (Eq. (1h)).

In Eq. (1d), a Michaelis–Menten function of V_l is used to account for a larger effect of physical activity in the first year of the intervention [33,34], and the parameters ζ_3 and $k_{n,si}$ are set to replicate the average one-year and four-year improvement in S_I due to physical activity reported in [33,35]. An exemplary representation of the behavior of Eq. (1d) with a simulated exercise program of 60 minutes/session, 3 sessions/week at $u = 50\%$ (as in [33]), compared to the case in which no exercise is considered, is shown in Fig. 1, where $S_{I,target} = 0.18$ and $\tau_{SI} = 150$ days (i.e., simulating a rapid T2D progression). The example in Fig. 1 shows that an improvement in S_I of about 30% is observed at the end of the first year, in line with [33], whereas after four years the distance between the two curves falls below 8%. When the same exercise program is simulated by setting $\tau_{SI} = 180$ days, (i.e., a slower trend for T2D progression), a higher benefit on S_I is

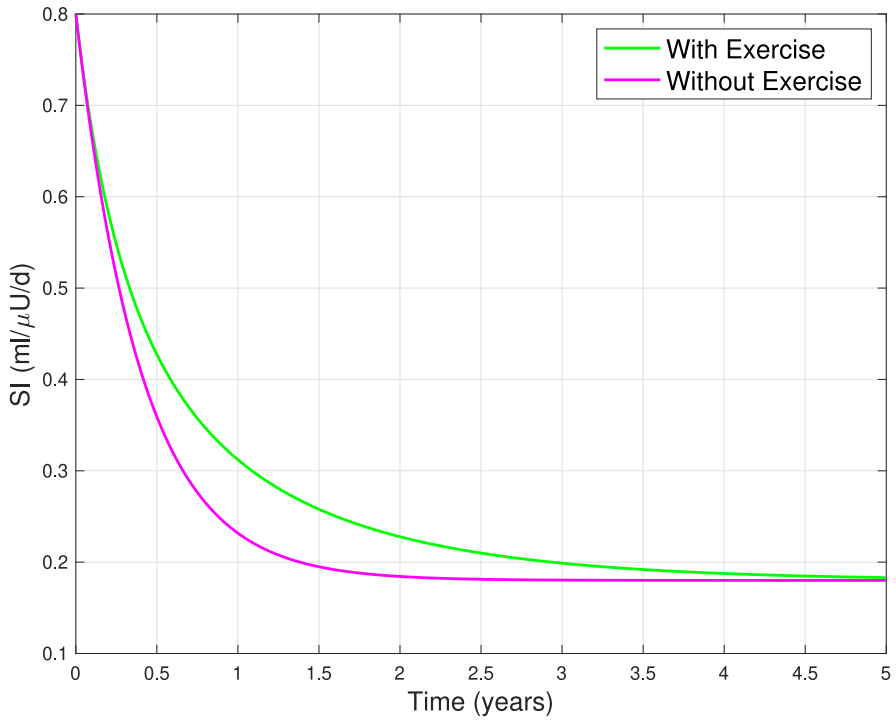


Fig. 1. Time trend of insulin sensitivity over a five-year horizon (simulation: 60 minutes/session, 3 sessions/week, $u = 50\%$, $S_{I,target} = 0.18$, $\tau_{SI} = 150$ days). The green curve shows the increase produced by the exercise with respect to the trend observed when no exercise is considered (magenta curve).

observed, specifically about 35% after one year and about 20% after four years, paralleling results shown by [35].

Regarding Eqs. (1a)–(1b) here introduced, the gains of the Hill functions ζ_1, ζ_2 and k_n are set in a way that a basal glucose concentration (G) value around 126 mg/dl is targeted after five years when the same exercise program simulated in Fig. 1 is considered, consistently with the results described in the Diabetes Prevention Program study [9]. Fig. 2 shows a comparison between the preliminary version of the model [29] and the model proposed in this study, at two different exercise intensities ($u = 20\%$ and $u = 50\%$). Specifically, Fig. 2 shows that the preliminary version of the model led to early saturation of the effects of physical activity on beta-cell mass dynamics. As such, the earlier, approximate model was not able to capture the effects due to varying duration or intensity of the exercise, leading to unrealistic reversal of diabetes for any exercise program, including those at low intensity. Conversely, the model here proposed shows different benefits for varying intensities, in line with the well-known dose–response relationship [31,36], as assessed in more detail in Section 2.2. For what concerns the modeling assumptions regarding insulin sensitivity decay, it is to note that while the simulation horizon extends to 20 years, the dynamics of S_I is built to reach its steady-state behavior within a shorter timescale, approximately within 6 years and is consistent with the response of this subsystem both in the presence of sustained physical activity and with no physical activity, as outlined both in modeling [16–18] and clinical studies [9,35,37]. Moreover, the 20-year horizon is here simulated to capture the long-term behavior of slower variables, such as beta-cell mass, whose adaptation in our modeling framework occurs over a longer time horizon [16]. In this regard, beta-cell growth and clearance coefficients are time-varying quantities, modeled as algebraic state-depending functions. Hence, the involved parameters are recalibrated according to the actual evolution of the state variables over the 20-year horizon.

2.2. Model simulations

The behavior of the proposed model was characterized by simulating a range of physical activity programs, as reported in the literature and in well-known T2D preventive guidelines. Specifically, the predicted benefits of physical activity were characterized by addressing four key aspects, i.e.: (i) the effect of varying exercise intensity; (ii) the effect of applying the World Health Organization (WHO) recommendations for chronic disease prevention; (iii) the effect of a discontinued exercise program, as presented in more detail in the following; (iv) the effect of inter-individual variability as detailed below.

All the simulations were carried out by supposing an exponential decay in insulin sensitivity S_I from 0.8 (at $t = 0$) to 0.18 (at $t = 5$ years) to simulate the onset of the conditions predisposing to T2D, as shown in Fig. 1. The time constant (τ_{SI}) was set to two different values, i.e.: $\tau_{SI} = 150$ days and $\tau_{SI} = 180$ days, to simulate different time courses of T2D progression [15,16]. The initial conditions for the variables G (mg/dl), I (μU/ml), β (mg), γ, and σ (μU/μg/day) were $[99.7604, 9.025, 1000.423, -0.00666, 536.67]$ respectively as in [16], whereas $PVO_2^{\max}$, G_{prod} (mg/kg/min), G_{up} (mg/kg/min), I_e (μU/ml/min), IL_6 (pg/ml), and Vl ((pg/ml)min) were initialized to 0, as in our previous work [29]. The rationale behind the choice of initializing to 0 all the variables related to the exercise is due to the fact that we are aimed at simulating virtual individuals that start undergoing an exercise program exactly at $t = 0$, with no exercise sessions experienced before.

2.2.1. Simulations of a regular exercise program with varying intensity

The existence of a dose–response relationship between the intensity of physical activity and the incidence of T2D is well known from the literature [36,37]. To assess the ability of the proposed model to predict the increased benefits of physical activity as a function of exercise intensity, simulations of an exercise program of three sessions/week, 60 minutes/session in a time window of 5 years, with u varying from 0% to 70% were performed to span the full range of light, moderate and vigorous intensity. In addition, the same training program was simulated on a time window of 20 years, considering only moderate and vigorous intensities ($u = 50\%$, 60%, and 70%).

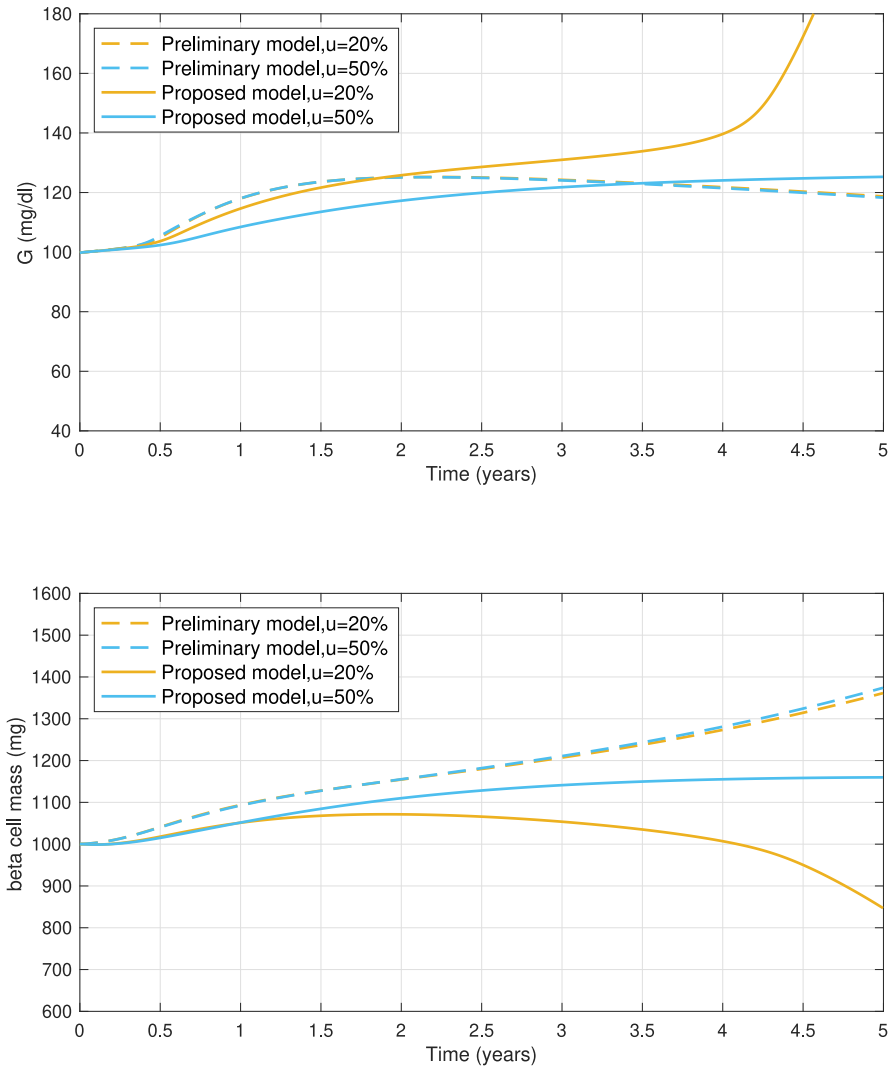


Fig. 2. Glucose concentration (top panel) and beta-cell mass (bottom panel) as a function of time obtained using the preliminary version of the model [29] (dotted lines) and the model here proposed (Equations (1), continuous lines) (simulation: 60 minutes/session, 3 sessions/week, $u = 20\%$ and 50%, $S_{I,target} = 0.18$, $\tau_{SI} = 150$ days).

2.2.2. Simulations of a regular exercise program following the WHO preventive recommendations

The WHO addressed the problem of preventing cardiovascular and chronic diseases through exercise by developing the following, equivalent recommendations [31]:

- at least 75 minutes/week of vigorous-intensity aerobic physical activity;
- at least 150 minutes/week of moderate-intensity aerobic physical activity.

Moreover, as suggested by [36], the benefit of moderate-intensity aerobic physical activity tends to saturate at about 400 minutes/week. To assess the ability of the proposed model to reflect the expected benefits of the WHO recommendations, the two suggested training programs were simulated by distributing the weekly duration into three sessions, lasting 25 and 50 min each, respectively. The variable u was set equal to 75% for vigorous intensity and equal to the 50% for moderate intensity, in line with [21].

In addition, to assess if the proposed model is able to replicate the expected saturation in benefit for moderate-intensity exercise observed for weekly duration equal to or higher than 400 minutes/week [36], simulations were performed for a total duration of 300, 350, 400, 450 and 500 minutes/week, equally distributed in three exercise sessions per week, by setting $u = 50\%$.

2.2.3. Simulations of a discontinued exercise program

The literature provides evidence that the benefits of exercise persist after the discontinuation of the intervention [7,32]. Specifically, in the Finnish Diabetes Prevention Study (FDPS) [7] adults with impaired glucose tolerance were involved in a four-year lifestyle intervention program that included moderately intense physical activity for a minimum of 30 min per day. Participants were followed for three more years after the intervention. Results outlined that the incidence rates of T2D and the basal glucose concentration values at the end of the intervention and in the post-intervention period varied only slightly, suggesting that beneficial lifestyle effects were maintained after the discontinuation of the intervention. Similar findings are described in the context of and the China Da Qing Diabetes Prevention Study (CDQDPS) [32,38]. Specifically, adults with impaired glucose tolerance were involved in a 20-year follow up, with lifestyle intervention (moderate intensity exercise, 2 sessions/day, 20 minutes/session) discontinued at the sixth year and benefits observed – in terms of reduced T2D incidence – up to 14 years after the intervention.

Scenarios similar to the ones described by the two abovementioned studies were simulated, specifically:

- for FDPS: moderate intensity exercise was simulated at three different values of u (30%, 40%, 50%), with daily sessions of 30 min. The exercise was interrupted at the fourth year, with a simulation horizon of seven years.
- for CDQDPS: moderate intensity exercise was simulated at three different values of u (30%, $40\%, 50\%$), with two exercise sessions per day, each lasting twenty minutes, as in suggested in Pan et al. [38]. The exercise was interrupted at the sixth year, with a simulation horizon of twenty years.

2.2.4. Simulations of inter-individual variability

To assess the capability of the model to reflect the heterogeneity across individuals in terms of T2D progression in response to physical activity, a series of simulations was performed to assess the sensitivity of the model output to perturbations in parameters and physical activity patterns, in three complementary scenarios, as detailed in the followings. Unless otherwise specified, the simulated exercise program consists of regular sessions performed at intensity $u = 60\%$ with three sessions per week each lasting 60 min. All the described simulations were run over a 20-year simulation horizon.

(1) Inter-individual variability in the genetic predisposition to T2D and environmental effects. To assess how possible physiological differences reflecting genetic predisposition to T2D and environmental effects may modulate disease progression and response to exercise intervention, we applied random independent uniform perturbations to a set of 18 model parameters (indicated in Table 1) and affecting Eqs. (A.1), (A.2), (A.3), (A.4), (A.5), (A.6), (A.13), (A.14), (A.15), (A.16), (A.18). These parameters are associated with genetic and environmental factors influencing the individual predisposition to T2D.
Two virtual populations were simulated, each batch including 200 simulations:

- PA group undergoing a physical activity program;
- no PA group with no simulated exercise.

(2) Inter-individual variability of average dietary intake and metabolic balance. To assess the possible influence of average food intake and daily glucose fluctuations on the benefit of physical activity, we introduced random uniform perturbations of the parameter R_0 in Eq. (1h), which in diabetes progression models encodes the net balance of multiple metabolic contributions, such as basal hepatic glucose production, zero-order glucose uptake by tissues and the average daily effect of meals [15,16,39]. Specifically, R_0 was randomized uniformly within the range $[-10\%, 10\%]$ of its nominal value. Additionally, to account for natural circadian variations, we introduced a daily random disturbance in the range $[-10\%, 10\%]$ to the current glycemia value, consistently with physiological variability reported in literature (see [39] and references therein). Specifically, two virtual populations were simulated, each batch including 200 simulations:

- individuals with high risk predisposition (faster decay in S_I: $\tau_{SI} = 150$);
- individuals with moderate risk predisposition (slower decay in S_I: $\tau_{SI} = 180$).

(3) Inter-individual variability in response to exercise and exercise program adherence. To assess the possible influence of individual physiological variability in exercise effectiveness and individual behavioral variations in exercise implementation on the long-term benefits of exercise on T2D progression, two key aspects were addressed:

(a) to introduce inter-individual variability in the individual response to exercise, we applied random independent uniform perturbations of 12 model parameters (indicated in Table 2) inherently related to the inter-individual heterogeneity in responsiveness to exercise. More in detail, two virtual populations were simulated, each batch including 200 simulations:

- individuals with high risk predisposition ($\tau_{SI} = 150$);
- individuals with moderate risk predisposition ($\tau_{SI} = 180$).

(b) variability in exercise program structure and adherence rates, simulated by randomizing exercise intensity, duration, and period of the sessions by applying random independent uniform perturbations in the ranges indicated in Table 3. Moreover, changes in individual adherence to the program were simulated by varying the individual probability of skipping the exercise session. Specifically, the following virtual populations were simulated, each batch including 200 simulations:

- individuals with high risk predisposition ($\tau_{SI} = 150$), skipping probability $Pr = 10\%$;
- individuals with high risk predisposition ($\tau_{SI} = 150$), skipping probability $Pr = 15\%$;
- individuals with moderate risk predisposition ($\tau_{SI} = 180$), skipping probability $Pr = 10\%$;
- individuals with moderate risk predisposition ($\tau_{SI} = 180$), skipping probability $Pr = 15\%$;
- individuals with moderate risk predisposition ($\tau_{SI} = 180$), skipping probability $Pr = 35\%$.

To compare these sets of simulations with the reference exercise program (intensity $u = 60\%$ with three sessions per week each lasting 60 min) we define the *Cumulative Exercise Dose* (CED) as $\text{CED} = \sum_{i=1}^{N} u_i \cdot D_i$, where u_i and D_i represent the intensity and duration of the ith session, respectively and N is the total number of sessions over the simulation horizon.

Table 1
Parameter ranges used to simulate inter-individual variability in genetic predisposition to T2D and environmental effects. Parameters are included in Eqs. (A.1), (A.2), (A.3), (A.4), (A.5), (A.6), (A.13), (A.14), (A.15), (A.16), (A.18).

Parameter	Range
W	[50, 150]
SI_{target}	[0.17, 0.20]
Vol_G	[110, 130]
τ_{SI}	[130, 200]
G_{σ_+}	[75, 90]
E_{g0}	[1.3, 1.6]
V	[4.75, 5.25]
k	[500, 900]
τ_β	[7500, 9000]
τ_γ	[2, 3]
τ_σ	[235, 265]
α_M	[142, 158]
α_{ISR}	[1.14, 1.26]
P_{max}	[4.32, 4.77]
α_P	[39, 43]
A_{max}	[8.55, 10]
α_A	[0.42, 0.46]
A_b	[0.76, 0.85]

3. Results

3.1. Simulated effects of varying exercise intensity

The predictions obtained by simulating different exercise programs with varying intensity using the proposed model are shown in Fig. 3 for

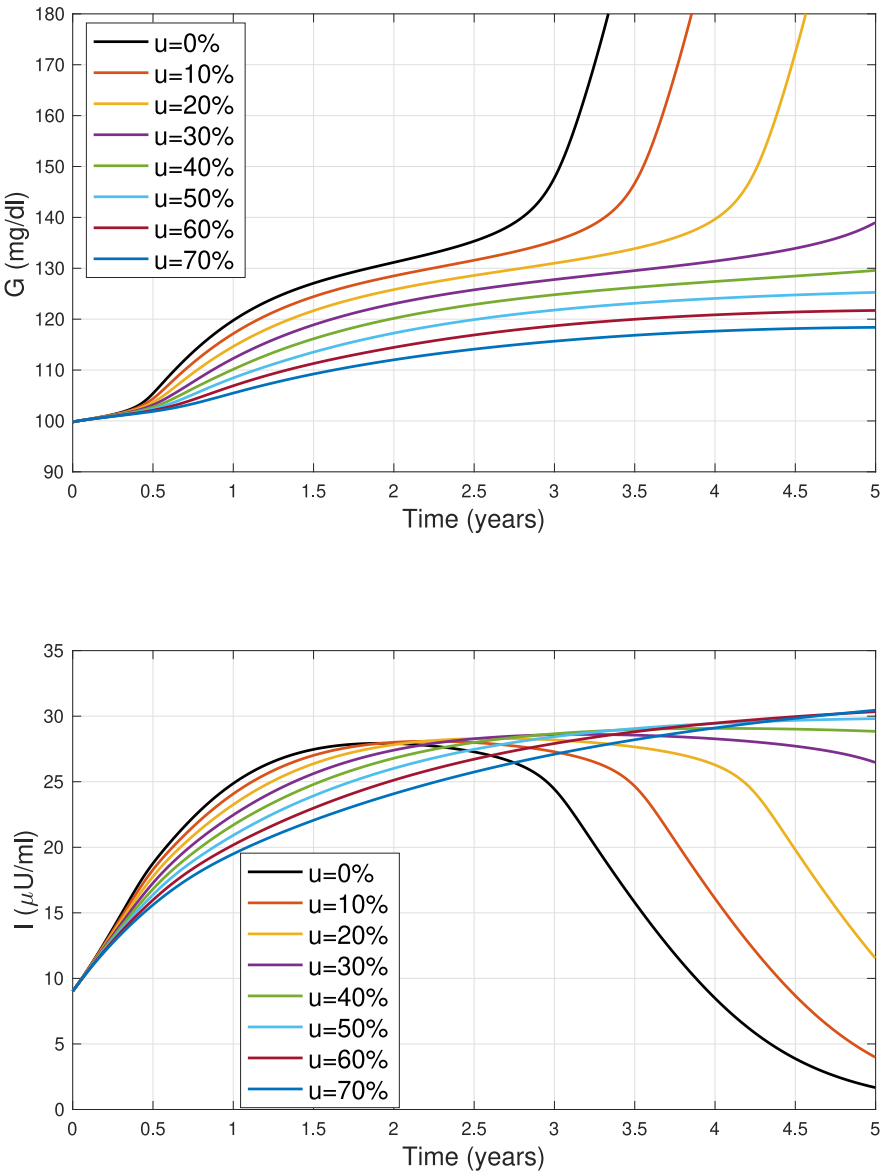


Fig. 3. Basal glucose concentration (top panel) and insulin concentration (bottom panel) as a function of u over a five-year simulation horizon (simulations: 60 minutes/session, 3 sessions/week, τ_{SI} = 150 days).

Table 2
Parameter ranges used to simulate inter-individual variability in response to exercise. Parameters are included in Eqs. (A.6), (A.8), (A.9), (A.10), (A.11), (A.12), (A.15), (A.16).

Parameter	Range
k_s	$[1.31\times10^{-6},\ 4.42\times10^{-6}]$
SR_{ex}	[0.04, 0.05]
k_m	[0.003, 0.005]
a_1	[0.0014, 0.0017]
a_2	[0.05, 0.062]
a_3	[0.0018, 0.0021]
a_4	[0.0437, 0.0534]
a_5	[0.0011, 0.0014]
a_6	[0.0675, 0.0825]
ζ_1	$[8.0\times10^{-5}, 1.2\times10^{-4}]$
ζ_2	$[8.0\times10^{-5}, 1.2\times10^{-4}]$
k_n	[900000, 1100000]
k_{nSI}	[4750000, 5250000]
ζ_3	[1.26, 1.54]

Table 3
Parameter ranges used to simulate inter-individual variability in the exercise program implementation.

Parameter	Range
Exercise intensity	[50%, 70%]
Session duration (minutes)	[30, 90]
Period between sessions (days)	{1, 2, 3}

τ_{SI} = 150 days on a five-year time span and in Table 4 for τ_{SI} = 150 and 180 days on a 20-year time span.

Fig. 3 shows that the benefit produced by exercise, as determined by lower values of G and higher values of I, increases with increasing u. In particular, simulations show that for $u \geq 50\%$ (i.e., moderate-to-vigorous intensity), G does not show the steep inflection that is observed for $u < 50\%$ and for no physical activity ($u = 0\%$). Moreover, for $u = 60\%$ and $u = 70\%$, G remains below the diabetic threshold of 126 mg/dl after five years. Table 4 shows that for τ_{SI} = 150 days and $u = 50\%$, G reaches the diabetic threshold after ten years, and then it

Table 4
Basal glucose and insulin concentration observed over a 20-year horizon for $u = 50\%$, 60%, and 70% and $\tau_{SI} = 150$ and 180 days.

		$G_{10-year}$ (mg/dl)	$G_{15-year}$ (mg/dl)	$G_{20-year}$ (mg/dl)	$I_{10-year}$ (μU/ml)	$I_{15-year}$ (μU/ml)	$I_{20-year}$ (μU/ml)
$u = 50\%$	$\tau_{SI} = 150$	128	$\gg$150	$\gg$150	29	< 3	< 3
	$\tau_{SI} = 180$	116	105	101	33	38	40
$u = 60\%$	$\tau_{SI} = 150$	117	108	101	33	36	39
	$\tau_{SI} = 180$	111	101	100	35	39	40
$u = 70\%$	$\tau_{SI} = 150$	112	102	100	35	39	40
	$\tau_{SI} = 180$	108	101	100	36	39	40

Table 5
Basal glucose levels observed in the simulated FDPS and CDQPS programs for $u = 30\%$, 40%, and 50% and $\tau_{SI} = 150$ and 180 days.

FDPS		$G_{4th-year}$ (mg/dl)	$G_{7th-year}$ (mg/dl)	CDQDPS		$G_{6th-year}$ (mg/dl)	$G_{20th-year}$ (mg/dl)
$u = 30\%$	$\tau_{SI} = 150$	131	>> 150	$u = 30\%$	$\tau_{SI} = 150$	133	>> 150
	$\tau_{SI} = 180$	126	136		$\tau_{SI} = 180$	125	>> 150
$u = 40\%$	$\tau_{SI} = 150$	127	>> 150	$u = 40\%$	$\tau_{SI} = 150$	124	123
	$\tau_{SI} = 180$	123	126		$\tau_{SI} = 180$	119	101
$u = 50\%$	$\tau_{SI} = 150$	124	128	$u = 50\%$	$\tau_{SI} = 150$	119	101
	$\tau_{SI} = 180$	120	121		$\tau_{SI} = 180$	115	100

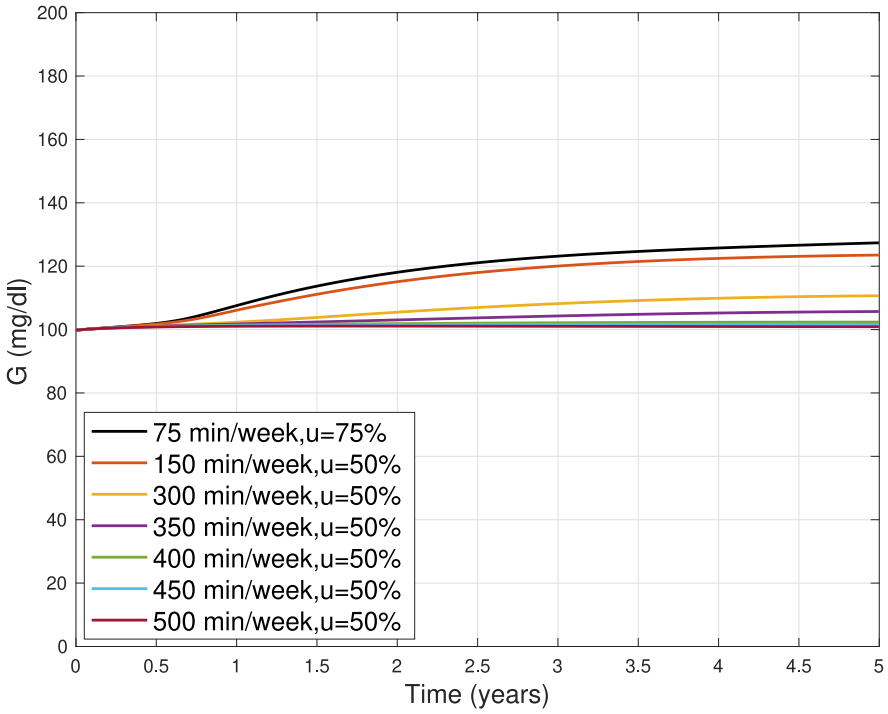


Fig. 4. Basal glucose concentration of vigorous exercise ($u = 75\%$) for 75 minutes/week and moderate exercise ($u = 50\%$) as a function of exercise duration, from 150 to 500 minutes/week, using $\tau_{SI} = 180$ days.

steeply increases. For higher values of u, no inflection is observed and G remains below the diabetic threshold in the whole simulation window, reaching values close to the healthy range (i.e., down to about 100 mg/dl). When a slower course of T2D is assumed (i.e., $\tau_{SI} = 180$), no inflection in G is observed with $u \geq 50\%$, G remains below the diabetic threshold and gets close to the healthy range after 20 years.

For what concerns basal insulin concentration (I), Fig. 3 shows that it reaches progressively higher values at $t = 5$ years as u increases, due to the increased beta-cell mass promoted by exercise. Over the 20-year horizon, when exercise is not sufficient to prevent T2D ($\tau_{SI} = 150$ days, $u = 50\%$), I progressively drops due to decreased beta-cell mass. Instead, when vigorous intensity exercise is simulated ($u = 60\%$, $u = 70\%$), I increases and, thus, G decreases down to values close to the healthy range. Specifically, I reaches a steady state condition around 40 μU/ml, whenever a basal glucose concentration of 100 mg/dl is restored. Overall, these results suggest that T2D onset could be delayed with a regular physical activity program of three sessions/week, 60 minutes/session at moderate or vigorous intensity, and that increased benefit is observed with increasing intensity, in line with the well-known dose–response relationships reported in the literature [31,36].

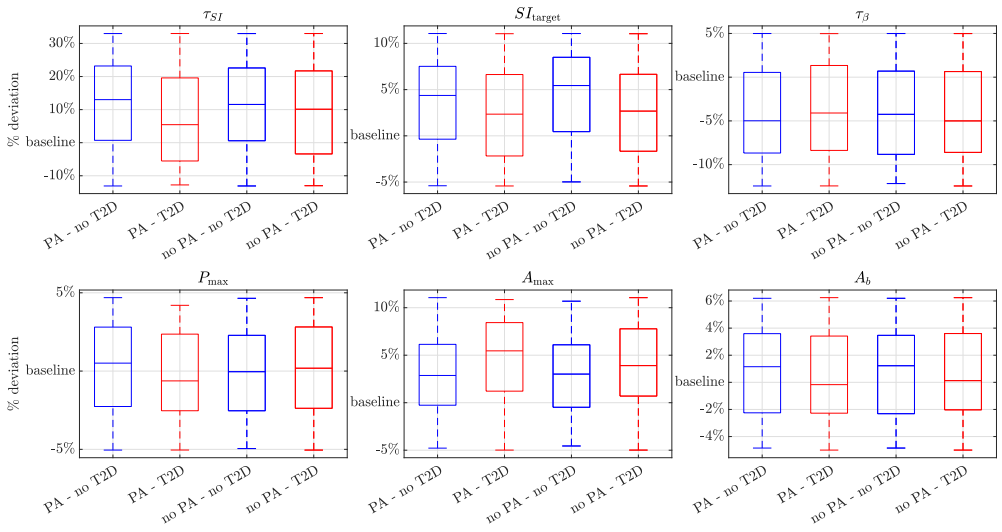


Fig. 5. Distribution of six out of 18 parameters related to genetic predisposition and environmental effects (i.e., τ_{SI}, SI_{target}, τ_β, $P_{\max}$, $A_{\max}$, A_b) in Simulation set 1. Variation is expressed as percentage change from the nominal value.

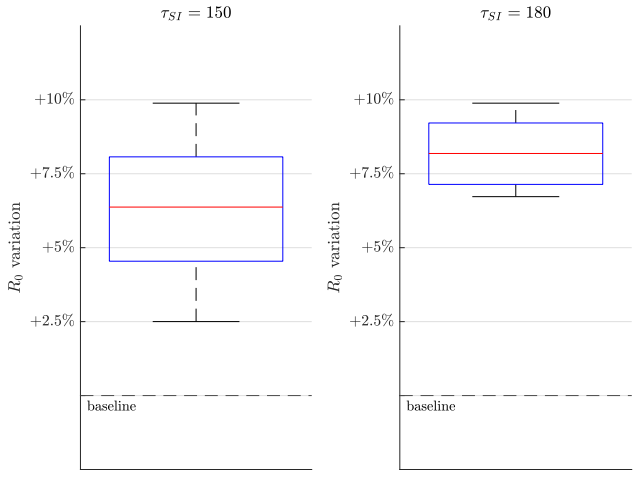


Fig. 6. Distribution of R_0 variation in T2D subjects with high ($\tau_{SI} = 150$) and moderate ($\tau_{SI} = 180$) baseline risk in Simulation set 2. Variation is expressed as percentage deviation from the nominal value of R_0.

3.2. Simulated effects of WHO recommendations

Fig. 4 shows the trend in G observed by simulating the WHO preventive recommendations for cardiovascular and chronic disease prevention [31] on a five-year horizon. The curves of the two minimum recommendations (i.e., vigorous-intensity physical activity for 75 minutes/week and moderate-intensity physical activity for 150 minutes/week) remain very close to each other for the whole duration of the simulation,in line with the equivalence of the two training programs reported by the WHO [31]. It should be noted that the small difference between the observed G values at the fifth year (i.e., 4 mg/dl) is negligible and that even smaller differences could be observed if slightly different values of u are used (i.e, higher values of u for moderate physical activity, lower values of u for vigorous physical activity). Fig. 4 also shows that, if the weekly duration of moderate-intensity exercise is increased up to 500 minutes/week, G further decreases and the observed benefit almost saturates at weekly duration of 400 min or higher, fully in line with findings from the literature [36].

3.3. Simulated effects of de-training in diabetes prevention studies

Table 5 presents the values of G obtained by simulating the FDPS and the CDQDPS programs. As for the simulated FDPS, following the interruption of the intervention at the fourth year, the values of G are below or close to the diabetic threshold at the seventh year in three out of the six simulated cases, specifically in those cases where G was already below the diabetic threshold at the end of the intervention (i.e., $u = 40\%$, $\tau_{SI} = 180$ days; $u = 50\%$, $\tau_{SI} = 150$ and 180 days). In the other three cases, the values of G were in the diabetic range at the end of the four-year simulated training, and simulations point to uncontrolled values of G at the seventh year, suggesting irreversible disease progression.

Similar results are observed when the CDQDPS is simulated. Specifically, an irreversible increase in G is observed after discontinuation of exercise at $u = 30\%$, i.e., in those cases where G is already close to or in the diabetic range at the sixth year. In three cases ($u = 40\%$, $\tau_{SI} = 180$ days; $u = 50\%$, $\tau_{SI} = 150$ and 180 days), a complete reversal is observed, with G restoring to a normoglycemic condition at about 100 mg/dl at the end of the simulation window, whereas for $u = 40\%$ and $\tau_{SI} = 150$ days a significant delay is observed after 20 years, with G remaining almost stable and slightly below the diabetic threshold.

In general, for what concerns the simulated effects of de-training following a regular exercise program, Table 5 shows that (i) the higher the intensity u and the slower the decay of insulin sensitivity, the lower the values of G at the end of the intervention and at the end of the follow-up period, and (ii) when G is lower than the diabetic threshold at the end of the intervention, benefits can be maintained in the follow-up period, up to 14 years after the discontinuation, in line with clinical evidence [7,32].

3.4. Simulated effects of inter-individual variability

3.4.1. Genetic and environmental predisposition to diabetes

Table 6 - Simulation Set 1 summarizes the percentage of individuals in which G remains below the diabetic threshold in the whole time horizon (no-T2D), for both the intervention (PA) and control (no PA) groups. As shown, the percentage of no-T2D outcomes is substantially higher in the PA group (66%) compared to the no PA group (35%), with physical activity showing its overall benefits even in presence of simulated inter-individual variability. Given the reference physical activity pattern here simulated, which is aligned with the WHO recommendations for T2D prevention, a certain percentage of simulated

Table 6
Percentage of simulated individuals in which G remains below the diabetic threshold in the whole time horizon (no-T2D) when parameters related to inter-individual variability in Simulation Sets 1, 2, 3a and 3b are varied.

Simulation set	Group	no-T2D (%)
1	PA group	66%
	no PA group	35%
2	$\tau_{SI} = 150$	55%
	$\tau_{SI} = 180$	80%
3a	$\tau_{SI} = 150$	70%
	$\tau_{SI} = 180$	96%
3b	$\tau_{SI} = 150,\ pr = 10\%$	96%
	$\tau_{SI} = 150,\ pr = 15\%$	41%
	$\tau_{SI} = 180,\ pr = 10\%$	100%
	$\tau_{SI} = 180,\ pr = 15\%$	100%
	$\tau_{SI} = 180,\ pr = 35\%$	50%

individuals will not be able to prevent T2D, reflecting an influence of individual genetic and physiological aspects.

A selection of the parameters more directly influencing these long-term outcomes (i.e. τ_{SI}, SI_{target}, τ_{β}, $P_{\max}$, $A_{\max}$, and A_b) is shown in Fig. 5. Specifically, the distribution of these six parameters, expressed as percentage change relative to their nominal (baseline) value, is shown for the two outcomes (T2D and no-T2D) in the PA and no PA groups. For instance, focusing on the parameter τ_{SI}, simulated individuals who do not develop T2D tend to have higher values of τ_{SI} than those who develop T2D, as expected, but the distribution of τ_{SI} variation in the PA-T2D group is even lower than in the no PA-T2D group, suggesting that simulated individuals who developed T2D despite engaging in physical activity may have more unfavorable, particularly severe, risk predispositions (faster baseline T2D progression) compared to those in the inactive diabetic group (no PA-T2D). Similar patterns can be observed in the distribution of the other parameters, for example SI_{target}, $P_{\max}$, $A_{\max}$ (i.e., lower steady-state insulin sensitivity, lower beta-cells production rate and higher beta-cells death rate in the PA-T2D group), underscoring the protective effect that physical activity may provide across large spectrum of simulated a-priori risk profiles, potentially mitigating individual predisposition to T2D risk.

3.4.2. Dietary intake and metabolic balance

Table 6 - Simulation Set 2 summarizes the percentage of no-T2D individuals at the end of the simulation horizon, for the two levels of T2D risk here simulated, low ($\tau_{SI} = 150$) and moderate ($\tau_{SI} = 180$). It can be observed that variability in dietary intake and metabolic balance may lead to variability in long-term outcomes when the same physical activity pattern is simulated, and this impact turns out to be significantly depending on the initial risk predisposition. For example, in simulated individuals with faster initial T2D progression ($\tau_{SI} = 150$), about one in two individuals may still develop T2D despite the regular exercise, confirming that changes in diet and fluctuations in glucose levels may limit the benefits of physical activity, particularly in those with higher initial risk.

Fig. 6 shows the distributions of the parameter R_0 across the T2D simulated subjects, expressed as percentage variation with respect to the nominal value. In the high-risk cohort ($\tau_{SI} = 150$), the distribution is centered at lower values and exhibits a wider spread compared to the moderate-risk group ($\tau_{SI} = 180$). This behavior of the model suggests a consistent trend and a compensation between physical activity and dietary intake: when the speed of T2D progression is slower and the risk is moderate ($\tau_{SI} = 180$), only individuals with higher dietary and metabolic load tend to be develop T2D in presence of exercise intervention, whereas a lower dietary load may be sufficient in individuals with higher baseline risk to compensate the benefits of physical activity and lead to T2D onset.

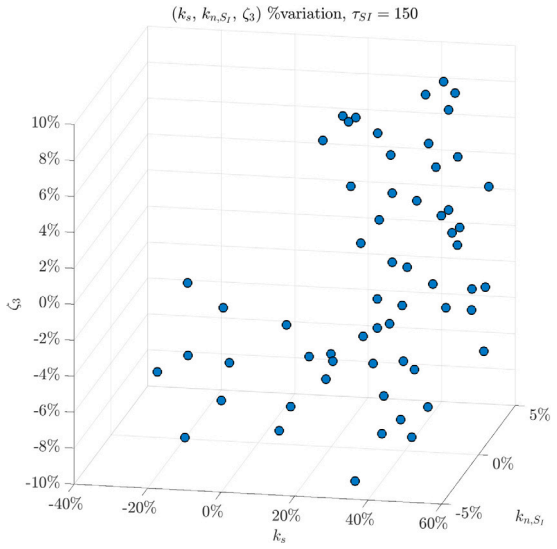


Fig. 7. Distribution of the variations of $k_s, k_{n.S_I}, \zeta_3$ in simulated individuals with T2D at the end of the simulation window in Simulation set 3a. Variations are expressed as percentage deviation from the nominal values of the parameters.

3.4.3. Response to exercise and program adherence

Table 6 - Simulation Set 3a shows the percentage of no-T2D individuals for the high risk ($\tau_{SI} = 150$) and moderate risk predisposition ($\tau_{SI} = 180$). The success rate of the exercise program proves to be high in both simulated populations, with a moderately higher percentage observed in the case of $\tau_{SI} = 180$, in line with the lower baseline risk in this simulated cohort. These results suggest that the intervention retains its preventive impact across a spectrum of individual responsiveness to exercise, though individuals with a more favorable physiological predisposition may benefit more.

Fig. 7 illustrates the 3D scatter plot of the percentage deviation of three out of 14 parameters (i.e., $k_s, k_{n.S_I}, \zeta_3$), among simulated individuals with T2D and with $\tau_{SI} = 150$. The plot shows a tendency of the majority of data points to cluster near a surface associated with approximately +40% variation of the parameter k_s, which governs the individual decay rate of exercise benefits (i.e., the higher k_s, the faster the decay of benefits following an exercise session, the lower the progressive benefits of regular sessions), indicating that faster decay of exercise may lead to higher risk regardless the value of $k_{n.S_I}$ and ζ_3 that govern the benefits of physical activity on SI. Some data points in Fig. 7 are characterized by values of k_s lower than 40%, but these correspond to values of negative variation of ζ_3 indicating that slower rates of decay of exercise benefit may still lead to a higher risk if combined with values of ζ_3 significantly lower than its nominal value, i.e., in individuals in which SI does not improve following physical activity, indicating that a severe drop in SI can hardly be compensated by physical activity alone. Therefore, inter-individual differences in how long the metabolic effects of exercise last and in how much physical activity can improve (or worsen) the decay in insulin sensitivity may drive failure in managing diabetes progression under the same training conditions.

Table 6 - Simulation Set 3b shows the percentage of simulated individuals who do not develop T2D when the intra-individual variability in exercise program and adherence is introduced. Results show that behavioral variability can strongly affect intervention effectiveness in individuals with different baseline risk conditions, particularly when adherence is considered. With low session dropout probability, the effectiveness of the simulated exercise program remains high regardless the value of τ_{SI}, despite the fluctuations introduced in intensity, duration, and period of exercise. Indeed, a small increase in the skipping

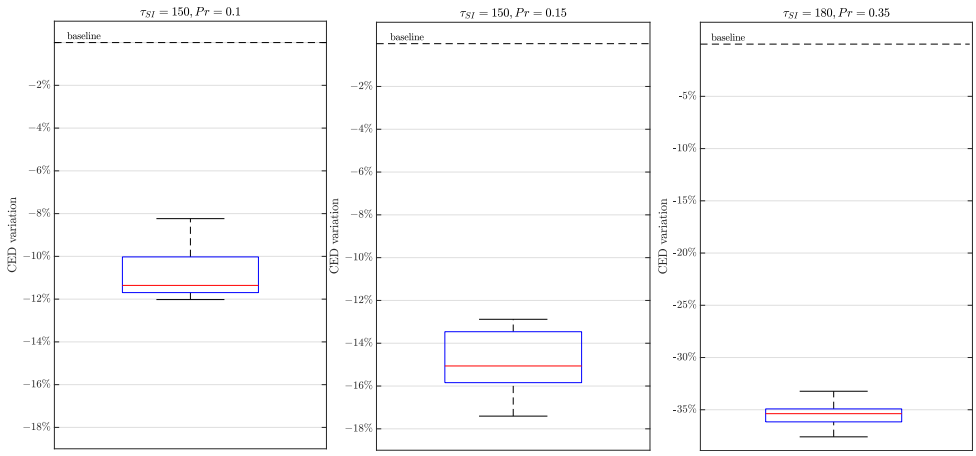


Fig. 8. Distribution of the CED variation for simulated individuals with T2D at the end of the simulation window in Simulation set 3b. Variation is expressed as percentage deviation from the dose of the nominal training program, for $\tau_{SI} = 150$, $Pr = 0.1$ (left panel) and $\tau_{SI} = 150$, $Pr = 0.15$ (center panel) and $\tau_{SI} = 180$, $Pr = 0.35$ (right panel).

probability from 10% to 15% in simulated individuals with $\tau_{SI} = 150$ induces a drop in success rate from 96% to 41%, whereas in the case of $\tau_{SI} = 180$ the success rate drops only with substantially higher session dropout probability. This highlights that moderate-risk individuals may have a more robust resilience to irregular adherence rates if a limited number of sessions is skipped, whereas when the skipping probability rises to 35% one out of two simulated individuals still develops T2D, suggesting that even in more favorable baseline risk conditions, excessive non-adherence may compromise the exercise intervention effectiveness. These findings are confirmed by the results in Fig. 8, that show the distributions of the CED variations (expressed as percentage deviation from the CED associated with the baseline exercise program) for the three cases $\tau_{SI} = 150, Pr = 0.1$, $\tau_{SI} = 150, Pr = 0.15$, $\tau_{SI} = 180, Pr = 0.35$ in simulated individuals who develop T2D. As expected, the CED follows a linear pattern with respect to the increase of the skipping probability, with higher session dropout rates corresponding to larger reductions in CED. The distributions are relatively narrow, confirming a limited effect of the parameter fluctuations.

4. Discussion

The model presented in this study has been shown to predict the trends of glucose and insulin concentration in individuals in the early phases of T2D progression – as modeled by an exponential decay in insulin sensitivity – undergoing regular physical exercise. To the best of our knowledge, the proposed model is the first in the literature able to precisely describe the cumulative benefits of physical activity on beta-cell function and insulin sensitivity and therefore on glucose–insulin regulation, as mediated by IL-6 released during exercise. Compared to an earlier, approximate model [29], the model here presented incorporates more realistic dynamics of insulin sensitivity, in line with [33,35] (Fig. 1), and is able to properly describe the effect of varying exercise intensity on beta-cell mass and basal glucose concentration (Fig. 2). The predictions of the model in a range of simulated conditions are aligned with findings reported in the literature and with evidence from clinical guidelines, as shown in Figs. 3–4 and in Tables 4–5. Specifically,the model accurately captures the dose–response relationship [36,37,40], and the model predictions show that the risk of developing T2D decreases as the exercise intensity increases, all the other parameters (weekly duration, τ_{SI}, initial conditions) being equal (Fig. 3, Tables 4–5). Moreover, the same benefit is predicted with moderate intensity exercise for 150 minutes/week and with vigorous-intensity exercise for 75 minutes/week (Fig. 4), in line with recommendations by the WHO [31], the American Diabetes Association [41] and the American College of Sports Medicine [42]. Saturation of benefits at around 400 minutes/week [36] for moderate-intensity physical activity is also adequately predicted (Fig. 4).

Moreover, the proposed model was also able to predict a maintained benefit following discontinuation of the intervention, as outlined in Table 5, in line with the findings from the FDPS and CDQDPS. It is worth noting that in the FDPS [35] the average basal glucose concentration observed in the group of participants who developed T2D was 126 mg/dl at the fourth year. This value is accurately approximated by our model as the average value of $G_{\text{4th-year}}$ in the conditions in which T2D eventually occurs is equal to 127 mg/dl (fist three rows in Table 5). Similar consistence was observed for the simulated CDQDPS training and de-training experiment. The results reported in Table 5 seem to capture the different T2D incidence scenarios and basal glucose concentration levels reported in the work by Li et al. [32]. In some cases, T2D develops at the sixth year or along the 20-year simulation, and in some other cases T2D is substantially slowed down or even reversed. Interestingly, Table 5 shows that (i) the higher the intensity u and the slower the drop in S_I, the lower the predicted values of G at the end of the intervention and at the end of the follow-up period; and (ii) when G is lower than the diabetic threshold at the end of the intervention, benefits are maintained in the follow-up period – up to 14 years after the discontinuation – if a moderate-intensity exercise program has been performed for six years.

Overall, the present work provides promising results as the proposed model is consistent with a range of clinical findings. In addition to the studies discussed above (e.g., [7,32,36]), there is ample literature reporting similar benefits of physical activity on diabetes progression (e.g., [8,9,43]), as such the model predictions seem to be realistic simulations of the average trend of a general “virtual subject” undergoing a lifestyle intervention for diabetes prevention. The model predictions show the benefits of regular exercise on diabetes progression also when populations of virtual subjects are simulated by means of random parameter perturbations. Indeed, when inter-individual variability in predisposition to T2D and environmental effects and diet variability is simulated, the model predictions prove to be aligned with evidence from clinical studies, suggesting on average 30%–60% reduction in T2D incidence via exercise with respect to individuals not performing physical activity, [7,9,38,43–45]. Notably, with reference to the simulated virtual population associated with inter-individual variability in genetic and environmental predisposition, it is worth noting that our results are in line with the evidence in [46], which assess a benefit around 74% in T2D incidence reduction even in people with high genetic risk. It should be noted that, although the model does not explicitly account for ethnicity, parameters related with genetic and environmental predisposition can be inherently associated with demographics as highlighted

by clinical studies (see for instance the outcomes in [32,43] related to the different insulin resistance levels in subjects from Asia with respect to the US DPP cohort [9]). While the current manuscript focuses also on inter-individual variability through parameter perturbations, the question of variability in the initial conditions of the state variables has been specifically addressed in a separate work [47]. In [47] we have proposed a counterfactual inference method to assess the effects of personalized physical activity plans on T2D and we systematically explored a large set of heterogeneous initial conditions, representing diverse metabolic states across individuals with the aim of identifying diverse sets of counterfactual physical activity plans. When variability in individual adherence and exercise program structure is introduced, the proposed model predicts that physical activity may still retain preventive benefits, with variable success rates, mainly depending on the degree of adherence and therefore on the average cumulative dose of exercise. This finding mirrors the evidence in [9,48] showing that even intermittent or irregular activity patterns may significantly reduce T2D risk. This supports the model's ability to capture variability in predictions with varying individual behavior. The model sets the basis to the development of methods suitable to tailor interventions to individual fitness levels and individual variability. In this regard, the model presented in this work has been applied for the design of a personalized intervention method in two recent works [39,49]. In those works, we proposed and validated a preliminary model-based state-feedback control scheme [49] and a more comprehensive output-feedback control design [39] based on Model Predictive Control approaches, for dynamically adjusting physical activity programs based on current individual conditions. These methods explicitly account for subject-specific characteristics, including genetic and metabolic variability, enabling the model to inform adaptive interventions. However, the study has some limitations that need to be addressed in the future. For instance, an important one is related to the lack of explicit modeling of meals, of the balance between caloric intake and expenditure as in [18,50], of detailed meal-by-meal dynamics and physiological changes related to diet, for example changes in glucose/insulin dynamics, changes in body weight, changes in the effects of physical activity and caloric expenditure due to changes in body mass composition. Another limitation involves the lack of explicit modeling of demographic and comorbidity-specific contributions, of biomechanical constraints and pharmacological treatments. Moreover, in this study a relatively rapid drop in insulin sensitivity was simulated, modeling the onset of conditions predisposing to T2D at $t = 0$. In future studies, it will be important to investigate the benefits of physical activity in healthy individuals at low risk of T2D (for example, by introducing different modeling approaches for the decay of insulin sensitivity and by modeling different individual fitness levels) to address the key role of exercise in early T2D prevention [15,51,52]. Importantly, the presented results are mainly simulation-based evidence. To allow a broader generalizability of the findings, future works will be aimed at overcoming the aforementioned limitations and at assessing the direct validation of the model predictions against data. Overall, these developments could pave the way to a more comprehensive personalization of model predictions in a range of scenarios to support the development of targeted recommendations for effective monitoring and prevention of T2D.

5. Conclusion

The role played by physical activity in delaying or preventing of T2D is well known and regular exercise can help reduce the burden this serious disease, which is forecast to represent a huge challenge worldwide [1]. What makes exercise *crucial* in T2D prevention is its beneficial effect that contributes to preserve beta-cell function, which is actually one of the key factors for diabetes prevention [27,28]. This work could represent an important step forward towards a quantitative description of the benefits promoted by exercise programs on T2D progression. Future research, for example integration of the effects of diet, incorporation of more complex models of individual risk, and model personalization will help improve the model and its ability to support the development of personalized recommendations for T2D prevention and support patients in reaching their healthy lifestyle targets with substantial potential benefits for patients and healthcare systems.

CRediT authorship contribution statement

Pierluigi Francesco De Paola: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Alessandro Borri:** Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Conceptualization. **Fabrizio Dabbene:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization. **Karim Keshavjee:** Writing – review & editing, Validation, Supervision. **Pasquale Palumbo:** Writing – review & editing, Methodology, Investigation. **Alessia Paglialonga:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

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Declaration of Generative AI and AI-assisted technologies in the writing process

Generative AI and AI-assisted technologies have not been utilized in the writing process, nor have they been used to create or alter any images included in this work.

Declaration of competing interest

None Declared

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Appendix

Full Model equations:

$$\frac{dG}{dt} = R_0 - \left(Eg_0 + S_I \cdot I\right) G + \frac{W}{Vol_G}(G_{\text{prod}} - G_{\text{up}}) \tag{A.1}$$

$$\frac{dI}{dt} = \beta \frac{ISR}{V} - kI - I_e \tag{A.2}$$

$$\frac{d\beta}{dt} = \frac{(P_{ISR} - A_{M_G})\beta}{\tau_\beta} \tag{A.3}$$

$$\frac{d\gamma}{dt} = -\frac{(\gamma - \gamma_{\infty,G})}{\tau_\gamma} \tag{A.4}$$

$$\frac{d\sigma}{dt} = -\frac{(\sigma - \sigma_{ISR_{M\infty}})}{\tau_\sigma} \tag{A.5}$$

$$\frac{dS_I}{dt} = -\frac{(S_I - S_{I,\text{target}})\left(1 - \zeta_3 \frac{V_l}{k_{n,S_I} + V_l}\right)}{\tau_{S_I}} \tag{A.6}$$

$$\frac{dPVO_2}{dt} = -0.8PVO_2 + 0.8u \tag{A.7}$$

Table A.1
Parameters of the model.

Parameter	Value	Unit
ks	$\frac{-\log(0.8)}{8\times7\times1440}$	1/min
W	70	kg
SI_{target}	0.18	[ml/μU/d]
SR_{ex}	0.045	[pg/ml/min]
k_m	0.004	[min]
Vol_G	117	[dl]
a_1	0.00158	[mg/kg/min^2]
a_2	0.056	[1/min]
a_3	0.00195	[mg/kg/min^2]
a_4	0.0485	[1/min]
a_5	0.00125	[mg/kg/min^2]
a_6	0.075	[1/min]
τ_{SI}	see Section 2 (Methods)	[d]
G_{σ_s}	75	[mg/dl]
R_0	864	[mg/dl/d]
Eg_0	1.44	[1/d]
V	5	[L]
k	700	[1/d]
τ_γ	2.14	[d]
τ_σ	249.9	[d]
τ_β	8570	[d]
k_M	2	dimensionless
α_M	150	[mg/dl]
k_{ISR}	2	dimensionless
α_{ISR}	1.2	dimensionless
P_{max}	4.55	dimensionless
k_P	4	dimensionless
α_P	41.77	[μU/μg/d]
A_{max}	9	dimensionless
k_A	6	dimensionless
α_A	0.44	dimensionless
A_b	0.8	dimensionless
γ_{max}	0.2	dimensionless
γ_s	99.9	dimensionless
γ_n	1	dimensionless
γ_0	0.1	dimensionless
$\sigma_{\text{ISR}_{\text{max}}}$	600	[μU/μg/d]
$\sigma_{\text{ISR}s}$	0.1	dimensionless
$\sigma_{\text{ISR}n}$	0.1	dimensionless
$\sigma_{\text{ISR}k}$	1	dimensionless
σ_b	3	[μU/μg/d]
$\sigma_{M_{\text{max}}}$	1	dimensionless
σ_{M_s}	0.2	dimensionless
σ_{M_n}	0.02	dimensionless
σ_{M_k}	0.2	dimensionless
ζ_1	10^{-3}	dimensionless
ζ_2	10^{-3}	dimensionless
ζ_3	1.4	dimensionless
k_n	10^6	[(pg/ml)*min]
k_{n,S_I}	$5 * 10^6$	[(pg/ml)*min]

$$\frac{dG_{\text{prod}}}{dt} = a_1 PVO_2 - a_2 G_{\text{prod}} \tag{A.8}$$

$$\frac{dG_{\text{up}}}{dt} = a_3 PVO_2 - a_4 G_{\text{up}} \tag{A.9}$$

$$\frac{dI_e}{dt} = a_5 PVO_2 - a_6 I_e \tag{A.10}$$

$$\frac{dIL_6}{dt} = SR_{\text{ex}} PVO_2 - k_m IL_6 \tag{A.11}$$

$$\frac{dV_l}{dt} = IL_6 - k_s V_l \tag{A.12}$$

State depending functions:

$$M_G = \frac{G^{k_M}}{G^{k_M} + \alpha_M^{k_M}} \tag{A.13}$$

$$ISR = \sigma \frac{(M_G + \gamma)^{k_{\text{ISR}}}}{(M_G + \gamma)^{k_{\text{ISR}}} + \alpha_{\text{ISR}}^{k_{\text{ISR}}}} \tag{A.14}$$

$$P_{ISR} = P_{\text{max}} \frac{ISR^{k_P}}{ISR^{k_P} + \alpha_P^{k_P}} \left(1 + \frac{\zeta_1 V_l^2}{k_n^2 + V_l^2}\right) \tag{A.15}$$

Table A.2
Description of the model state variables.

Symbol	Description	Unit
G	Plasma glucose concentration	[mg/dl]
I	Serum insulin concentration	[μU/ml]
β	Beta cell mass	[mg]
γ	Shift in glucose response	(dimensionless)
σ	Insulin secretion capability	[μU/μg/d]
S_I	Insulin sensitivity	[ml/μU/d]
PVO_2	Sovrabasal oxygen consumption	(dimensionless)
G_{prod}	Rate of incremental hepatic glucose production promoted by exercise	[mg/kg/min]
G_{up}	Rate of incremental glucose uptake by working tissues promoted by exercise	[mg/kg/min]
I_e	Rate of incremental insulin removal induced by exercise	[μU/ml/min]
IL_6	Concentration of IL-6 in the muscle compartment	[pg/ml]
V_l	Integral effect of physical activity representing the long-term effect of exercise	[(pg/ml)*min]

$$A_{M_G} = (A_{\text{max}} \frac{M_G^{k_A}}{M_G^{k_A} + \alpha_A^{k_A}} + A_b)\left(1 - \frac{\zeta_2 V_l^2}{k_n^2 + V_l^2}\right) \tag{A.16}$$

$$\gamma_{\infty,G} = \frac{\gamma_{\text{max}}}{1 + \exp\left(-\frac{(G-\gamma_s)}{\gamma_n}\right)} - \gamma_0 \tag{A.17}$$

$$M_\sigma = \frac{(G - G_{\sigma_s})^{k_M}}{\alpha_M^{k_M} + (G - G_{\sigma_s})^{k_M}} \tag{A.18}$$

$$ISR_\sigma = \sigma \frac{(M_\sigma + \gamma)^{k_{\text{ISR}}}}{(M_\sigma + \gamma)^{k_{\text{ISR}}} + \alpha_{\text{ISR}}^{k_{\text{ISR}}}} \tag{A.19}$$

$$\sigma_{\text{ISR}_\infty} = \frac{\sigma_{\text{ISR}_{\text{max}}}}{1 + \sigma_{\text{ISR}k} \exp\left(-\frac{(ISR_\sigma - \sigma_{\text{ISR}s})}{\sigma_{\text{ISR}n}}\right)} \tag{A.20}$$

$$\sigma_{M_\infty} = 1 - \frac{\sigma_{M_{\text{max}}}}{1 + \sigma_{Mk} \exp\left(-\frac{(M_\sigma - \sigma_{Ms})}{\sigma_{Mn}}\right)} \tag{A.21}$$

$$\sigma_{\text{ISR}_{M_\infty}} = \sigma_{\text{ISR}_\infty} \sigma_{M_\infty} + \sigma_b \tag{A.22}$$

The description of the variables is provided in Table A.2.

As for the state depending functions, reference is made to [16].

The values of the parameters, defined as in [16,21,29], are listed in Table A.1.

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